to a change in transference numbers of the potassium and chloride ions in the solution being measured. They demonstrated this effect by observing a potential drop across two calomel electrodes, one immersed in the suspension, the other in the supernatant liquid.

To eliminate this error, an equilibrium mixture of amphetamine sulfate and sodium stearate was centrifuged to remove the suspended material. The pH was again determined and found to be 8.6, which is in reasonable agreement with the calculated value, 8.49, from Eq. 4.

From these results it is proposed that Eq. 3 is descriptive of the system, and that the role of basic lubricants is the removal of hydrogen ion to promote the base-catalyzed browning of lactose. These findings coupled with later tests using inorganic alkalies indicate that the reaction is a general base-catalyzed reaction and not limited to amine bases.

It should be noted that the pH values shown in Fig. 1 are those of suspensions and contain the errors discussed above.

Results of this work furnish a practical means for predicting discoloration of tablets containing lactose with a few short-term tests. It is suggested that a new formulation be tested simply by preparing a solution or slurry of the ingredients, placing it in a bath at 60° for 2 or 3 days, and then observing the color. In this way one can determine whether the formulation is satisfactory before preparing tablets. Also, it is demonstrated that lactose should not be utilized in combination with bases, and when lactose is combined with amine salts, alkali stearates and talc should be avoided.

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Synthesis of α- and β-Amino Ketone Analogs of Amino Acids as Antibacterial Agents

By SHU-SING CHENG[†], SIGURDUR JONSSON[‡], and FRED T. SEMENIUK

α- and β-Amino ketone analogs of amino acids were synthesized as potential antagonists of amino acids in microbial metabolism. The hypothetical mechanism of antibacterial activity for certain analogs is proposed. The successful use of organocadmium reagents for the synthesis of the aliphatic and aromatic series of α- as well as β-amino ketones indicates a wider scope of applicability than by the method of Dakin-West or by Friedel-Crafts acylation. These series of compounds show antimicrobial activity *in vitro*.

THE ANTIBACTERIAL activity (1) reported for β-amino ketone analogs of β-alanine suggested that α-amino ketone analogs of α-amino acids might possess similar activity. Due to the structural similarity between amino ketone analogs and the natural amino acids, one may assume that these analogs function as antagonists to amino acids, thus interfering with biochemical reactions in which individual amino acids or related peptides participate.

The cell walls of most Gram-positive bacteria consist primarily of components linked together as the following sequence: 3-O-carboxyethylhexosamine-*dl*-alanine-*d*-glutamic acid *l*-lysine-*dl*-alanine-*dl*-alanine (2). It could be assumed that an amino ketone analog of α-alanine would interfere with the formation of this peculiar amino-sugar peptide, thus inhibiting the cell wall synthesis. Many species of bacteria are able to grow on simple media containing ammonium and other inorganic salts, plus a single organic carbon source such as glucose. Some species require the addition of certain amino acids, simple peptides, and vitamins for growth. It is obvious that many bacteria can synthesize a majority of amino acids from ammonium salt and glucose. Two ways are recognized by which a bacterium can assimilate ammonia and convert it to α-amino groups in amino acids. These are the fumarate and the α-ketoglutarate pathways (3). The fumarate pathway is dependent upon a condensation reaction between fumaric acid and ammonia to yield aspartic acid. The α-ketoglutarate pathway is

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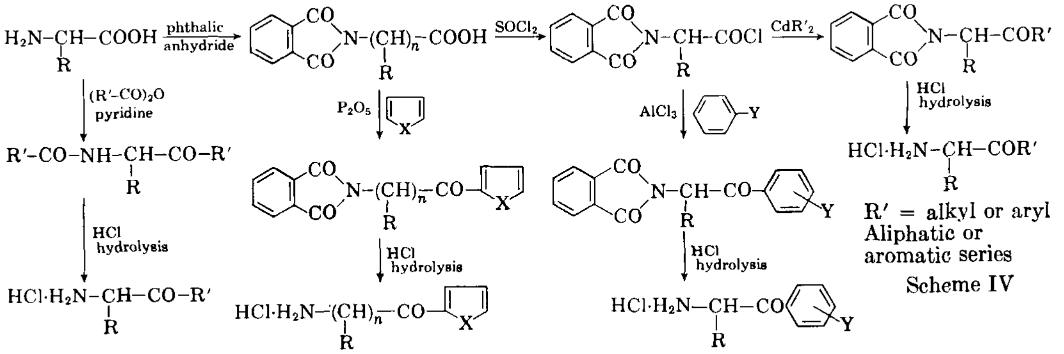


Aliphatic series
Scheme I

X = O, S
n = 1, R = H or alkyl
n = 2, R = H
Heterocyclic series
Scheme II

Y = H, alkyl, halogen hydroxyl
Aromatic series
Scheme III

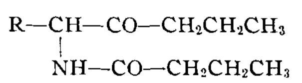
R' = alkyl or aryl
Aliphatic or aromatic series
Scheme IV

based upon a reaction involving α-ketoglutarate and ammonia, the product being *l*-glutamic acid. Both aspartic and glutamic acids can serve as an amino group "pool" from which various amino acids are derived through transamination reaction between the pool and a variety of α-keto acids under the catalysis of transaminases. It follows that amino ketone analogs of aspartic acid or glutamic acid would block the formation of most amino acids.

Glycine combines with cysteine and glutamic acid to yield a tripeptide, γ-glutamylcysteinylglycine (glutathione). Glutathione functions as an important prosthetic group in the enzyme glyceraldehyde-3-phosphate dehydrogenase (4) which catalyzes the dehydrogenation and phosphorylysis of glyceraldehyde-3-phosphate, thus converting it to 1,3-diphosphoglyceric acid in the anaerobic breakdown of glucose (5). The amino ketone analogs, H_2NCH_2COR, of glycine conceivably might condense with cystein and glutamic acid to form a pseudo tripeptide, $HOOCCH(NH_2)CH_2CH_2CONHCH(CH_2SH)CONHCH_2COR$, with a ketone fragment instead of a carboxyl group at one end of the peptide chain. This analog of glutathione might compete with glutathione for the enzyme glyceraldehyde-3-phosphate dehydrogenase. In this fashion, the conversion of glyceraldehyde-3-phosphate to 1,3-diphospho-glyceric acid is preventable, and the microbial utilization of glucose may be interrupted. Phenylalanine, tyrosine, and leucine have been shown to be essential amino acids for the growth of psittacosis virus in chick embryo tissue (6). Presumably, amino ketone analogs of these amino acids might inhibit the growth of this virus. In addition to the proposed hypothetical mechanism for the antibacterial activity of each particular amino acid, the amino ketone analogs might interfere with peptide formation in protein synthesis in general.

Most of the aliphatic and aromatic amino ketone analogs of glycine, α-alanine, leucine, phenylalanine, tyrosine, and aspartic acid were synthesized by the hydrolysis of acylamido or phthalimido ketones obtained by the Dakin-West method or by Friedel-Crafts acylation, respectively. The heterocyclic β-aminoethyl ke-

TABLE I.—α-ACYLAMIDO KETONES

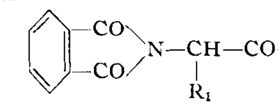


$$R-\underset{NH-CO-CH_2CH_2CH_3}{CH}-CO-CH_2CH_2CH_3$$

R	M.P., °C.	Yield, %	Formula	Analyses[a] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
$CH_3-\underset{CH_3}{CH}-CH_2-$	b.p. 265 $n^{29°}$ 1.4618	35	$C_{13}H_{25}NO_2$	68.9	69.0	11.1	10.98	6.17	6.70
$C_6H_5-CH_2-$	63-64	28	$C_{16}H_{23}NO_2$	73.5	74.0	8.85	8.73	5.37	5.25
$p-HO-C_6H_4-CH_2-$	108-109	39	$C_{16}H_{23}NO_3$	70.8	69.8	8.35	8.64	5.05	4.88

[a] Analyses by Weiler and Strauss, Oxford, England.

TABLE II —α-PHTHALIMIDO KETONES



R_1	R_2	M.P., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Cl or Br, % Calcd.	Cl or Br, % Found
H	p-Cl—C_6H_4—	216–217	61	$C_{16}H_{10}ClNO_3$	64.05	63.82	3.37	3.28	4.67	4.67	11.81	11.68
H	p-Br—C_6H_4—	227–228	33	$C_{16}H_{10}BrNO_3$	55.9	56.0	2.95	3.08	4.08	3.69	23.1	22.8
H	n-C_7H_{15}—	56–57		$C_{17}H_{21}NO_3$	71.00	70.85	7.34	7.41	4.86	4.69		
H	p-CH_3—C_6H_4—	186–187	32 { 18	$C_{17}H_{13}NO_3$	73.09	72.70	4.69	4.88	5.02	5.07		
H	o-CH_3—C_6H_4—	130–131	14	$C_{17}H_{13}NO_3$	73.09	73.30	4.69	4.62	5.02	4.82		
H	3,4-diCH_3—C_6H_3—	165–166	70	$C_{18}H_{15}NO_3$	73.69	74.0	5.16	5.11	4.78	4.54		
H	C_6H_5—	167–168	84	$C_{16}H_{11}NO_3$	72.43	73.20	4.15	4.11	5.30	5.10		
CH_3—	C_6H_5—	87–88	85	$C_{17}H_{13}NO_3$	73.0	73.46	4.66	4.91	5.02	4.93		
CH_3—	p-CH_3—C_6H_4—	110–111	53	$C_{18}H_{15}NO_3$	73.69	73.78	5.16	5.24	4.78	4.84		
CH_3—	3,4-diCH_3—C_6H_3—	114–115	57	$C_{19}H_{17}NO_3$	74.01	75.0	5.58	5.53	4.56	4.26		
$HOOCCH_2$—	C_6H_5—	220–221		$C_{18}H_{13}NO_5$	67.0	66.66	4.05	4.22	4.34	4.22		
$HOOCCH_2$—	p-CH_3—C_6H_4—	187–188		$C_{19}H_{15}NO_5$	67.7	67.14	4.47	4.85	4.15	4.20		
$C_6H_5CH_2$—	n-C_6H_{13}—	86–87	15	$C_{23}H_{25}NO_3$	76.2	75.96	6.95	6.58	3.85	3.80		

[a] Analyses by Weiler and Strauss, Oxford, England.

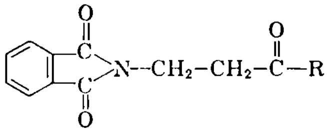
tone analogs of β-alanine were synthesized by the hydrolysis of phthalimido ketones obtained from the condensation of thiophene or furan and β-phthalimido-propionic acid under the catalysis of phosphorus pentoxide. These heterocyclic analogs have not been reported previously.

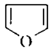
The adaptation of organocadmium reagent by Cheng and Jonsson (1) for the preparation of alkyl β-aminoethyl ketones proved feasible. It therefore seemed of some interest to study the possibility of utilizing this reagent for the preparation of α-amino ketone analogs of amino acids.

The above mentioned amino ketone analogs were prepared as summarized by the reaction schemes. In scheme I, the aliphatic series of α-amino ketones are prepared by the hydrolysis of acylamido ketones, obtained conveniently by heating an α-amino acid with an aliphatic acid anhydride in pyridine according to Dakin and West (7). Since excessive amounts of acid anhydride are required for the formation of the acylamido ketone, the high cost of the higher member acid anhydride would render the preparation of acylamido ketone impractical. Furthermore, alkyl aminomethyl ketones are not attainable by the treatment of glycine with acid anhydride in pyridine. Glycine is subject to decomposition by the action of acetic anhydride and its higher homologs after a short period of heating in pyridine. These difficulties encountered in the synthesis of amino ketone analogs of α-amino acids by the Dakin-West method were overcome by the use of organocadmium reagent as illustrated in scheme IV.

In scheme III, the aromatic series of α-amino ketones are prepared by the hydrolysis of phthalimido ketones obtained from the condensation of phthalimidoacyl chlorides and aromatic hydrocarbons under the catalysis of anhydrous aluminum chloride according to Friedel-Crafts acylation reaction. The yields range from 60 to 80%. Unfortunately this reaction failed to yield β-phenyl α-phthalimidopropiophenone when β-phenyl α-phthalimidopropionyl chloride was treated with anhydrous aluminum chloride in dry benzene, 2-phthalimido-1-indanone being obtained instead. This unexpected compound was formed from the intramolecular acylation of the β-phenyl nucleus by the acyl carbonyl of the same molecule. The tendency of five-membered ring closure was so pronounced that the competitive intermolecular acylation reaction was overwhelmed, so that the expected product was not formed. A study of the factors which govern the pattern of the reactions reveals the operation of the inductive as well as of the

TABLE III.—β-PHTHALIMIDOETHYL KETONES



R	M.P., °C.	Yield,[a] %	Formula	Analyses[b]							
				C, %		H, %		N, %		S, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
	148	35	$C_{15}H_{11}NO_4$	66.88	67.50	4.13	4.23	5.21	5.45		
	154–155	38	$C_{15}H_{11}NO_3S$	62.30	63.30	5.22	4.72	4.84	4.85	11.08	10.88

[a] Based on the quantity of β-phthalimidopropionic acid consumed. [b] Analyses by Weiler and Strauss, Oxford, England.

mesomeric effects. The difficulty however, in obtaining the desired intermediate for the preparation of β-phenyl-α-aminopropiophenone was overcome by the use of organocadmium reagent as outlined in scheme IV, where R is a benzyl and R′ phenyl, respectively.

The successful preparation of aliphatic and aromatic series of α-amino ketone analogs of amino acids by the use of organocadmium reagent demonstrates the wide scope of applicability and the advantage of this method over that of the Dakin-West method and of Friedel-Crafts acylation. 1-Phenyl-2-phthalimido-3-nonanone was prepared in a yield of 15%, comparable with 14–20% for the alkyl β-phthalimidoethyl ketones prepared from β-phthalimidopropionyl chloride by the same method (1). This reveals that the bulky α-phthalimido as well as the β-phenyl group exerts no steric hindrance on the condensation of the phthalimidoacyl chloride with either the alkyl or aryl organocadmium reagent.

The isolation of biphenyl from a reaction using phenylcadmium for the preparation of β-phenyl-α-phthalimidopropiophenone reveals the decomposition of organocadmium reagent in the course of reaction. This probably accounts for the low yield of amino ketone prepared by this method. The probable formation of the aliphatic hydrocarbons has not been demonstrated, perhaps due to the high volatility of the alkanes. The overall yield of amino ketones prepared by this method ranges from 20 to 40%, whereas it ranges from 32 to 34%, and 40 to 50% by Dakin-West and Friedel-Crafts methods, respectively.

These series of α- and β-amino ketones have been found to be active *in vitro* against the growth of bacteria and fungi when tested by the serial broth dilution and agar diffusion methods. The results of *in vitro* screening will appear in a subsequent paper.

EXPERIMENTAL

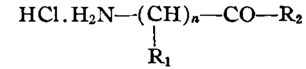
The chemical procedures used for the preparation of the various intermediates and products are illustrated by the following examples:

Phthalimidocarboxylic Acids.—Phthalimidoacetic, α-phthalimidopropionic, β-phthalimidopropionic, β-phenyl-α-phthalimidopropionic, and phthaloylaspartic acids were prepared according to Gabriel's method (8), with modification in the process of purification as described for β-phenyl-α-phthalimidopropionic acid: 100 Gm. of *dl*-phenylalanine (0.60 mole) and 90 Gm. phthalic anhydride (0.60 mole) were melted together at 210°, and the melt was maintained at this temperature for one-half hour. The product was cooled to room temperature and then dissolved in 150 ml. alcohol by refluxing. White crystalline powder, 165 Gm., was obtained after the solution was cooled to room temperature, corresponding to a yield of 82%. Recrystallization from alcohol gave large rhombic crystals, m.p. 177–178°.

Phthalimidoacyl Chlorides.—Phthalimidoacetyl, α-phthalimidopropionyl, β-phenyl-α-phthalimidopropionyl, and phthaloylaspartyl chlorides were prepared by the procedure described for β-phenyl-α-phthalimidopropionyl chloride: a mixture of 110 Gm. β-phenyl-α-phthalimidopropionic acid (0.5 mole), and 148 Gm. thionyl chloride (1.24 moles) was refluxed until all the solid dissolved. The excess thionyl chloride (25 ml.) was recovered by distillation under reduced pressure. The dark brown residue from the distillation was repeatedly extracted with petroleum ether (30–60°) by refluxing. A 102-Gm. quantity of chloride was obtained, corresponding to a yield of 85%, m.p. 73°.

Aliphatic Series of Acylamido Ketones. (See Table I).—4-Butyramido-2-methyl-5-octanone, 1-phenyl-2-butyramido-3-hexanone, 1-(p-hydroxy)phenyl-2-butyramido-3-hexanone were prepared by the procedure described for 1-(p-hydroxy)phenyl-2-butyramido-3-hexanone: a mixture of 10 Gm. of *dl*-tyrosine (0.055 mole), 300 ml. pyridine, and 43 ml. of n-butyric anhydride was refluxed for 8 hours. The excessive n-butyric anhydride and pyridine were removed by distillation under reduced pressure. The residual liquid was poured, with stirring, into 400 ml. petroleum ether (b.p. 30–60°). Six grams of 1-(p-hydroxy)phenyl-2-butyramido-3-hexanone was isolated, corresponding to a yield of 39%. It melted

TABLE IV.—α- AND β-AMINO KETONE HYDROCHLORIDES



$$HCl.H_2N\text{—}\underset{R_1}{\underset{|}{(CH)}}_n\text{—}CO\text{—}R_2$$

						Analyses[a]							
						C, %		H, %		N, %		Cl, %	
n	R_1	R_2	M.P., °C.	Yield, %	Formula[b]	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	C_6H_5—	186[c]	78	C_8H_9NO	56.0	55.8	5.85	5.77	8.18	8.29		
1	H	p-$CH_3C_6H_4$—	206[c]	82	$C_9H_{12}NO$	58.2	57.6	6.51	6.44	7.55	7.38		
1	H	o-$CH_3C_6H_4$—	160[c]	76	$C_9H_{12}NO$	58.2	57.4	6.51	6.77	7.55	7.15		
1	H	3,4-di$CH_3C_6H_3$—	213[c]	76	$C_{10}H_{14}NO$	60.2	60.13	7.03	7.28	7.01	7.3	17.7[f]	17.2
1	H	p-ClC_6H_4—	279–280[c]	69[d]	C_8H_8ClNO	46.5	47.1	4.36	4.42	6.81	6.82	34.5[g]	35.0
1	H	p-BrC_6H_4—	285[c]	74[d]	C_8H_8BrNO	38.5	39.0	3.63	3.80	5.60	5.80		
1	H	n-C_7H_{15}—	157–159	51	$C_9H_{19}NO$	55.85	55.0	10.4	10.1	7.24	7.42	18.25[f]	18.80
1	$CH_3\text{—}\underset{CH_3}{\underset{\mid}{CH}}\text{—}CH_2$—	n-C_3H_7	89–90	62	$C_9H_{19}NO$	55.95	56.08	10.4	9.99	7.24	6.83		
1	CH_3	C_6H_5—	183–184[c]	48	$C_9H_{11}NO$	58.2	57.7	6.49	6.90	7.56	7.70		
1	CH_3	p-$CH_3C_6H_4$—	232[c]	63	$C_{10}H_{13}NO$	60.1	59.88	7.09	7.15	7.01	7.24		
1	CH_3	p-HOC_6H_4—	206–208[c]	33	$C_9H_{11}NO_2$	53.80	53.85	6.01	6.48	6.96	6.50		
1	CH_3	3,4-di$CH_3C_6H_3$—	180[c]	14	$C_{11}H_{15}NO$	61.9	61.5	7.55	7.71	6.58	6.32		
1	$C_6H_5CH_2$—	n-C_3H_7—	127–128	43	$C_{12}H_{17}NO$	63.2	62.36	7.93	8.03	6.14	6.18	15.59	15.95
1	$C_6H_5CH_2$—	n-C_6H_{13}—	108–109	27	$C_{15}H_{23}NO$	66.95	66.10	8.97	8.61	5.20	5.40	13.4	14.0
1	$C_6H_5CH_2$—	C_6H_5—	215–216[c]	22[e]	$C_{15}H_{15}NO$	68.9	68.23	6.18	6.13	5.35	5.35	13.59	13.95
1	$C_6H_5CH_2$—	p-$CH_3C_6H_4$—	207[c]	14[e]	$C_{16}H_{17}NO$	69.7	68.65	6.58	6.44	5.26	4.95	12.81	13.20
1	$HOOCCH_2$—	C_6H_5—	204[c]	71	$C_{10}H_{11}NO_3$	52.30	52.27	5.28	5.34	6.10	6.52		
1	$HOOCCH_2$—	p-$CH_3C_6H_4$—	198–199[c]	28	$C_{11}H_{13}NO_3$	54.40	54.38	5.80	5.74	5.76	5.59		
1	p-$HOC_6H_4CH_2$—	n-C_3H_7	147–148	22	$C_{12}H_{17}NO_2$	59.30	60.20	7.45	7.22	5.75	6.03		
2	H		173–174[c]	49	$C_7H_9NO_2$	48.00	48.10	5.76	5.63	8.06	8.00		
												S, %	
2	H		160–161	62	C_7H_9NOS	44.00	44.15	5.28	5.47	7.32	7.90	16.79	17.00

[a] Calculated as hydrochloride. [b] Formula of free amino ketone. [c] Melts with decomposition. [d] Yield based on the quantity of phthalimido ketone consumed. [e] Overall yield based on the quantity of phthalimidoacyl chloride used. [f] Cl% of the hydrochloride. [g] Cl%, including organic-bound Cl, of the hydrochloride.

at 108–109° after recrystallization from a mixture of benzene and petroleum ether.

Alkyl and Aryl α-Phthalimido Ketones (See Table II).—The aryl phthalimido ketones were prepared by Friedel-Crafts acylation, excepting β-phenyl-α-phthalimidopropiophenone, not obtainable by Friedel-Crafts acylation, which was prepared by the condensation of β-phenyl-α-phthalimidopropionyl chloride and phenylcadmium according to the procedure (1) described for the synthesis of alkyl β-phthalimidoethyl ketones. The procedure for the alkyl and aryl α-phthalimido ketones is essentially the same as that for the β-phthalimidoethyl ketones, except for the process of purification, as described for 1-phenyl-2-phthalimido-3-nonanone: the organocadmium reagent was prepared from 36.6 Gm. of *n*-hexyl bromide (0.22 mole), 5.3 Gm. magnesium turnings (0.22 mole), and 16 3 Gm. anhydrous cadmium chloride (0.22 mole) in anhydrous ether. After the solvent was replaced with dry benzene, 42 Gm. β-phenyl-α-phthalimidopropionyl chloride (0.134 mole) in benzene was added to the mixture. The reaction was completed and the product isolated in the usual way. The thick oil obtained after the removal of benzene was distilled under reduced pressure, yielding a yellowish oil at 70–240°/0.5 mm. Crystals, 7.6 Gm., were obtained from the alcoholic solution of the oil, corresponding to a yield of 15%. The crystals melted at 86–87° after two recrystallizations from alcohol.

Heterocyclic β-Phthalimidoethyl Ketones (See Table III).—2-Furyl, and 2-thienyl β-phthalimidoethyl ketones were prepared by the procedure described for 2-thienyl β-phthalimidoethyl ketone: a mixture of 22 Gm. β-phthalimidopropionic acid (0.1 mole) and 100 ml. dry benzene was refluxed for 1 hour with constant stirring. The mixture was cooled to room temperature, and 10 Gm. phosphorus pentoxide was added in one portion. The mixture was stirred for 1 hour at room temperature and then refluxed for 5 hours, following which it was filtered, and the filtrate washed successively with 10% sodium carbonate and water, and dried over anhydrous sodium sulfate. A syrupy liquid, obtained when the solvent was removed from the benzene solution, crystallized as a white powder, weighing 6.25 Gm. and corresponding to a yield of 37.5% based upon the quantity of β-phthalimidopropionic acid actually consumed (12.3 Gm.). The white powder crystallized from boiling alcohol as short needles, m.p. 154–155°.

Amino Ketone Hydrochlorides (See Table IV).—Amino ketone hydrochlorides were prepared by the hydrolysis of the phthalimido or the acylamido ketones in a mixture of glacial acetic and concentrated hydrochloric acids under refluxing conditions according to the procedure described in the previous paper (1).

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Solvolysis of Symmetrical and Mixed Aspirin Anhydrides in 75% Dioxane–25% Water

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The neutral solvolysis of aspirin anhydride, I, and the mixed anhydrides of aspirin and acetic acid, II, of acetylsalicoylsalicylic and acetic acids, III, have been studied as functions of temperature in 75% dioxane by volume so as to compare them with the literature values on *m*- and *p*-substituted benzoic anhydrides studied in the same solvent. There is very little change in the heats of activation but large increases in the frequency factors of the *ortho*, mixed or symmetrical, over the *meta* and *para*. The mixed anhydrides of an *o*-acylbenzoic acid and acetic acid have higher solvolysis rates by virtue of lower frequency factors than the symmetrical aspirin anhydrides.

RECENT STUDIES (1) have demonstrated the presence of all possible products of acyl transfer in a melt of aspirin anhydride, I. Identification of these products necessitated the synthesis of several mixed anhydrides of aspirin and aspirin derivatives with acetic acid, *viz.*, the mixed anhydride of aspirin and acetic acid, II, and the mixed anhydride of acetylsalicoylsalicylic acid and acetic acid, III.

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