Electrophilic Additions of Acyl and Sulfonyl Halides to 2-Ethoxypyridine 1-Oxide. A New Class of Activated Esters and Their Application to Peptide Synthesis[1]

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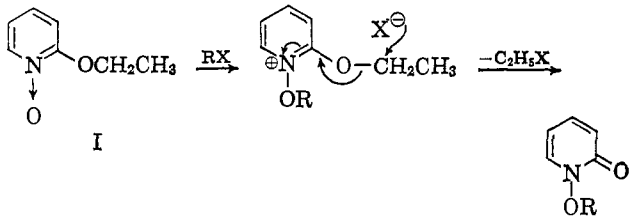
The condensation of 2-ethoxypyridine 1-oxide with carboxylic acid chlorides results in the ready liberation of ethyl chloride and the formation of carboxylate esters of 1-hydroxy-2(1H)-pyridone in good yields. These 2(1H)-pyridone derivatives were found to be a new class of activated esters and their high reactivity in nucleophilic reactions is demonstrated. The physical properties of the products are discussed. The application of this novel reaction to peptide synthesis is shown to proceed without racemization in the case of a phthaloyl dipeptide. The reaction of 2-ethoxypyridine 1-oxide with sulfonyl halides proceeds in a similar manner; illustrative reactions of the resulting sulfonate esters with nucleophilic reagents are given.

Since the pioneering efforts of Ochiai and his colleagues during the 1940's on the chemistry of pyridine N-oxides,[4] these substances and the related 1-alkoxypyridinium salts have rapidly developed into valuable intermediates for the synthesis of a large number of pyridine derivatives.[5,6] In a recent paper,[7] we reported that the reaction of 2-ethoxypyridine 1-oxide (I) with alkyl and aralkyl halides resulted in the formation of 1-alkoxy- and 1-aralkoxy-2(1H)-pyridones, respectively, in excellent yield. This process was envisioned as proceeding mechanistically by attack of the electrophilic halide at the N-oxide oxygen atom, followed by a nucleophilic attack by the halide ion with loss of ethyl halide to afford the observed product.



I

(1) Part XXI of the series on unsaturated heterocyclic systems. For paper XX see L. A. Paquette and T. R. Phillips, *J. Org. Chem.*, **30**, 3883 (1965).

(2) Alfred P. Sloan Foundation Research Fellow.

(3) Inquiries regarding this manuscript should be directed to the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.

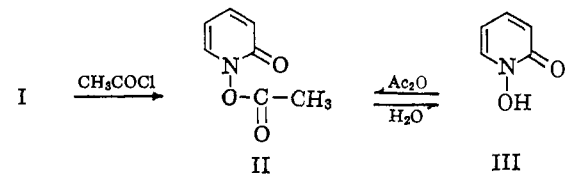
(4) This work has been summarized by E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(5) For recent reviews of this subject, see (a) E. N. Shaw, "Pyridine and Its Derivatives," Part Two, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, Chapter IV; (b) D. V. Ioffe and L. S. Eiros, *Russ. Chem. Rev.* (English Transl.), **30**, 569 (1961); (c) K. Thomas and D. Jerchel in "Neuere Methoden der Preparativen Organischen Chemie," Band III, W. Foerst, Ed., Verlag Chemie, Weinheim, Germany, 1961, p. 61; (d) A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and and Sons, Inc., New York, N. Y., 1960, pp. 61, 102; (e) A. R. Katritzky, *Quart. Rev.* (London), **10**, 395 (1956).

(6) For additional work of more recent origin, see (a) J. F. Vozza, *J. Org. Chem.*, 27, 3856 (1962); (b) L. Bauer and L. A. Gardella, *ibid.*, **28**, 1320, 1323 (1963), and references cited therein.

(7) L. A. Paquette, *Tetrahedron*, in press.

In an effort to extend the utility of I as a synthetic intermediate, an investigation of its reactivity toward acyl halides was undertaken.[8] Slow addition of I to excess acetyl chloride at room temperature produced an immediate evolution of a gas (ethyl chloride) to give, on evaporation of the excess acetyl chloride and recrystallization of the residue from ethyl acetate, an excellent yield of white prisms (II) with proper combustion analysis for $C_7H_7NO_3$. The ultraviolet absorption of this product at 228 and 302 mμ was in agreement with a 2(1H)-pyridone formulation. Its infrared spectrum, however, not only exhibited a band at 1665 cm.$^{-1}$, the frequency customarily associated with the 2(1H)-pyridone carbonyl, but, in addition, demonstrated a second carbonyl absorption at 1800 cm.$^{-1}$. If indeed the product was 1-hydroxy-2(1H)-pyridone acetate (II), then II must be an activated ester.[9] The problem remained to prepare II by an



II III

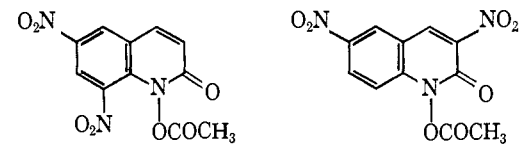
unequivocal route and this was conveniently achieved by acetylating 1-hydroxy-2(1H)-pyridone (III) with acetic anhydride.[11,12]

(8) A preliminary account of this work has appeared: L. A. Paquette, *J. Am. Chem. Soc.*, **87**, 1407 (1965).

(9) It is now well documented[10] that increased reactivity in nucleophilic reactions involving carbonyl groups is paralleled by a marked shift of the infrared absorption of the carbonyl bands toward shorter wave lengths.

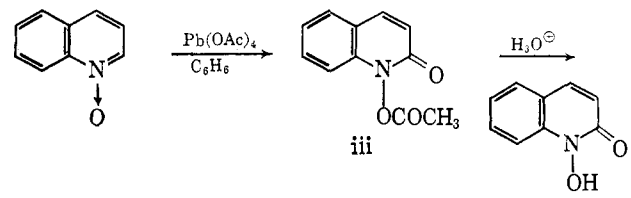
(10) For a concise summary of this topic, see H. A. Staab, *Angew. Chem. Intern. Ed. Engl.*, **1**, 351 (1961).

(11) Examination of the existing literature has revealed that the acetyl derivatives of two dinitro-1-hydroxycarbostyrils have been prepared by another route: C. Kaneko, *Yakugaku Zasshi*, **79**, 428 (1959). The infrared absorption frequencies of the acetyl groups of i and ii were reported to be located at 1812 and 1804 cm.$^{-1}$, respectively.



i ii

(12) A. Ohta and E. Ochiai, *Chem. Pharm. Bull* (Tokyo), **10**, 1260 (1962), have recently discussed the formation of iii from the lead tetraacetate oxidation of quinoline N-oxide and its acid hydrolysis to N-



iii

Table I. Benzoates of 1-Hydroxy-2(1H)-pyridone. Properties and Analytical Data

Compd. no.	R	σ	Benzoyl carbonyl absorption, cm.$^{-1}$	Pyridone carbonyl absorption, cm.$^{-1}$	Yield, %[a]	M.p., °C.	Recrystn. solv.	Reactn. proc.	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	*p*-CH_3O	−0.268	1770	1670	95.1	113–114.5	EtAc	A	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.61	4.91	5.62
V	3,4,5-$(CH_3O)_3$	...	1770	1670	98.4	130–132	EtAc	A	$C_{15}H_{15}NO_6$	59.01	4.95	4.59	58.72	5.11	4.32
VI	*p*-$(CH_3)_3C$	−0.197	1770	1665	93.4	124–125	EtAc	B	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.64	6.36	5.07
VII	*p*-CH_3	−0.170	1780	1670	87.0	165–166	EtAc	B	$C_{13}H_{11}NO_3$	68.11	4.84	6.11	67.80	4.85	6.05
VIII	H	0.000	1780	1670	92.4	140	EtAc	A	$C_{12}H_9NO_3$	66.97	4.22	6.51	66.64	4.20	6.43
IX	*m*-CH_3O	+0.115	1780	1670	73.8	112–113	EtAc	B	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.34	4.77	5.66
X	*p*-Cl	+0.226	1775	1670	93.5	147–148	EtAc	A	$C_{12}H_8ClNO_3$	57.73	3.23	5.61	57.77	3.24	5.47
XI	*m*-Cl	+0.373	1785	1665	51.0	116–119	EtAc	B	$C_{12}H_8ClNO_3$	57.73	3.23	5.61	57.91	3.27	5.55
XII	*m*-Br	+0.391	1783	1670	87.8	138–139	EtAc	A	$C_{12}H_8BrNO_3$	49.00	2.74	4.76	48.94	2.91	4.90
XIII	*m*-CF_3	+0.43	1790	1665	87.2	94–96	EtAc	A	$C_{13}H_8F_3NO_3$	55.13	2.85	4.95	55.03	2.87	5.02
XIV	*p*-CF_3	+0.54	1790, 1780	1690	83.8	131–131.5	EtAc	A	$C_{13}H_8F_3NO_3$	55.13	2.85	4.95	55.14	3.10	4.90
XV	*p*-CN	+0.600	1780	1665	69.0	164–165	EtAc	B	$C_{13}H_8N_2O_3$	65.00	3.36	11.66	64.69	3.49	11.46
XVI	*m*-NO_2	+0.710	1790	1680	82.4	136–138	EtAc	B	$C_{12}H_8N_2O_5$	55.39	3.10	10.77	55.22	3.12	11.16
XVII	*p*-NO_2	+0.778	1785	1670	84.0	150.5–151.5	EtAc	A	$C_{12}H_8N_2O_5$	55.39	3.10	10.77	55.17	2.92	10.93

[a] All yields were determined on the quantity of material obtained after one recrystallization of the crude ester from ethyl acetate.

A qualitative examination of the behavior of II in solvolytic reactions was next considered to determine if the reactivity suggested by the carbonyl infrared absorption could be observed experimentally.[13] Dissolution of II in purified water at room temperature resulted in the quantitative deposition of colorless crystals of III. Similar studies with *n*-butyl alcohol and *n*-butylamine (see the Experimental Section) resulted in the extremely facile transfer of the acetyl function from II to the particular substrate. This demonstration of the high reactivity of II in alcoholysis, hydrolysis, and ammonolysis places this class of compounds on a level comparable to acyl halides and anhydrides.

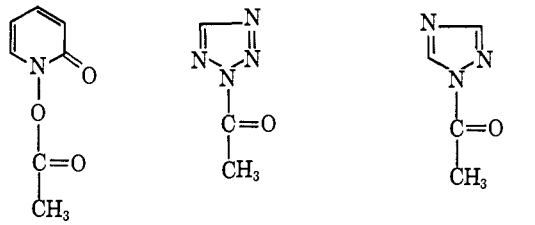
The reaction of I with acid chlorides was subsequently extended to a series of substituted benzoyl chlorides. Benzoyl halides seemed particularly suitable for this study since the selection of appropriate substituents on the benzoyl group would, in addition, also permit examination of the effect of electron density on the position of the infrared absorption of the resulting activated carbonyl function. Reaction of I with a wide variety of benzoyl halides afforded the corresponding esters in good to excellent yields; the results are tabulated in Table I. The evolution of ethyl chloride generally began upon admixture of the benzoyl halide with I and the reactions were routinely completed by warming on a steam bath for approximately 30 min. The esters were readily recrystallized from ethyl acetate and were all found to be crystalline.

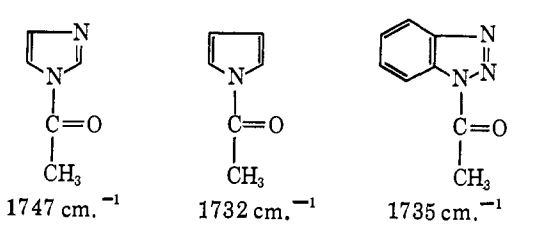
The benzoates are listed in Table I in the order of increasing σ-value for the benzoyl substituent.[15] Correlation of the activated carbonyl infrared frequencies with the substituent constant (and therefore with the electron density at that center) shows a satisfactory trend in the proper direction, although a more linear relationship would have been more desirable.[16] The ultraviolet absorption maxima for the various products are given in Table II.

Applications to Peptide Synthesis. The practical utility of highly reactive esters in the synthesis of peptides is widely known and has been extensively applied.[17] In recent years, *p*-nitrophenyl[18] and cyano-

hydroxycarbostyril. The acetyl group of iii displayed an infrared absorption band at 1800 cm.$^{-1}$.

(13) It is of interest to compare the carbonyl infrared absorption of II with those of the various "azolides" studied by Staab.[10] The shift of





the carbonyl band of the "azolides" toward shorter wavelengths, *i.e.*, the increase in the C—O force constant, has been attributed to the varied electron attraction by the respective heterocyclic rings.[14]

(14) H. A. Staab, W. Otting, and A. Ueberle, *Z. Elektrochem.*, **61**, 1000 (1957).

(15) The σ-values were taken from J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw Hill Book Co., Inc., New York, N. Y., 1962, p. 87.

(16) The infrared spectra were determined as Nujol mulls; in this medium crystalline aggregation has been known on occasion to affect the position of peak intensities. In retrospect, therefore, the spectra should have been determined in solution; unfortunately, however, samples of the various esters are no longer available to check out the possibility that a more linear correlation may exist with solution spectra.

(17) For reviews of this subject, see (a) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 1027–1048; (b) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **8**, 465 (1957); (c) W. Grassman and W. Wünsch, *Fortschr. Chem. Org. Naturstoffe*, **13**, 444 (1956).

(18) M. Bodanszky, *Ann. N. Y. Acad. Sci.*, **88**, 655 (1960).

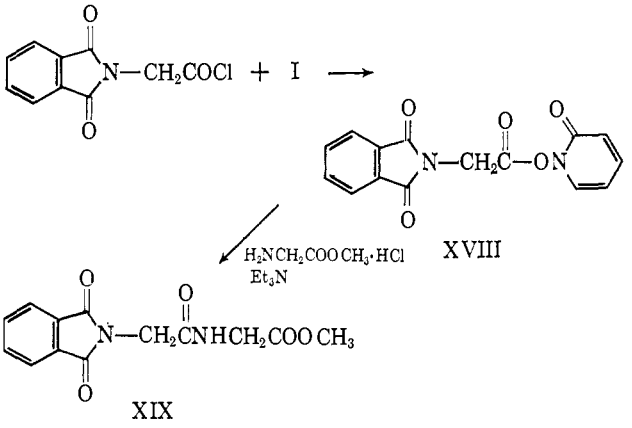
Table II. Ultraviolet Absorption Maxima for Esters of 1-Hydroxy-2(1H)-pyridone

Compd. no.	λ_{max}^{EtOH}, mμ (ε)[a]
II	228 (6850), 302 (5500)
IV	213 (17,300), 232 sh (5800), 266 (21,400), 304 sh (6300)
V	214 (34,600), 277 (12,650), 302 sh (9850)
VI	245 (20,150), 288 (5750), 298 (5950)
VII	245 (18,700), 287 sh (5850), 297 (6050), 304 sh (5850)
VIII	231 (18,900), 287 sh (5450), 297 (5700)
IX	213 (33,400), 244 (8970), 301 (8350)
X	244 (19,050), 276 sh (4050), 288 sh (5050), 299 (5600)
XI	229 (8250), 295 (2800)
XII	226 (15,400), 295 (5600)
XIII	226 (18,000), 271 sh (2250), 279 sh (3050), 304 (5050)
XIV	226 (20,050), 275 sh (2950), 284 sh (3850), 304 (5100)
XV	237 (24,700), 246 sh (18,850), 284 sh (5250), 293 (6250), 304 sh (5450)
XVI	220 (31,400), 255 (7950), 297 (6400)
XVII	231 (11,050), 258 (13,300), 296 (7150)

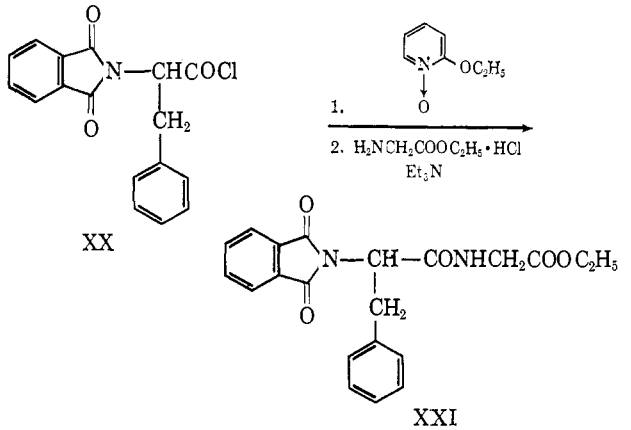
[a] All spectra were determined on freshly prepared solutions in order to minimize interaction with the solvent, especially in the more reactive cases.

methyl[19] esters have seen considerable service, but the need for better chemical methods of forming the peptide bond continues to be emphasized.[20] Disadvantages such as insolubility of by-products in water at neutral pH and the tedious nature of the active ester preparation have been cited. Since the time that this study was begun, the field of active esters based upon hydroxylamine derivatives has been under vigorous scrutiny with the expectancy that such compounds might possess more desirable properties. Esters of N-hydroxyphthalimide were the first to be reported,[21] and this promising lead has now been extended to include esters derived from N-hydroxysuccinimide,[22] oximes,[23] hydroxamic acids,[24] N-[25] and N,N-disubstituted hydroxylamines.[25,26]

In view of the ease with which esters of 1-hydroxy-2(1H)-pyridone can be formed in high yield (see above), and because such compounds meet the important requirements of high crystallinity and pronounced reactivity, their application to the construction of peptide units was examined. Furthermore, the expected by-product, 1-hydroxy-2(1H)-pyridone (III), is readily soluble in water which permits its facile removal. When phthalylglycyl chloride was treated with 2-ethoxypyridine 1-oxide (I), a *quantitative yield* of the activated ester XVIII resulted. This material proved to be highly crystalline, but attempts at its recrystallization induced decomposition. The crude ester, however, could be easily handled and condensation of this compound with glycine methyl ester in chloroform readily afforded phthalylglycylglycine methyl ester (XIX) in 85.3% yield. To investigate whether optically active amino acids could be activated by this procedure with retention of optical purity, phthaloyl-L-phenylalanyl chloride (XX) was condensed with I and there was



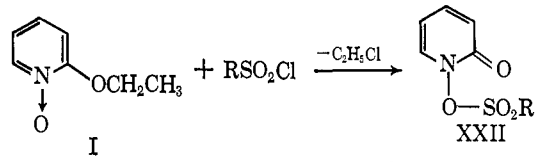
likewise obtained a *quantitative yield* of activated ester, which readily reacted with glycine ethyl ester to give a 79.7% yield (from XX) of optically pure phthaloyl-L-phenylalanylglycine ethyl ester (XXI), $[\alpha]^{29}D$ −145° (in EtOH).



Consequently, carboxyl activation of amino acids *via* 1-hydroxy-2(1H)-pyridone esters appears suitable for the synthesis of dipeptides and could find application in those cases where liberation of the elements of hydrogen chloride is not desirable.[27,28]

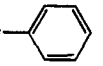
(19) R. Schwyzer, M. Feuer, and B. Iselin, *Helv. Chim. Acta*, **38**, 84 (1955).
(20) R. Schwyzer and P. Sieber, *Nature*, **199**, 172 (1963).
(21) G. H. L. Nefkens and G. I. Tesser, *J. Am. Chem. Soc.*, **83**, 1263 (1961); G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. trav. chim.*, **81**, 683 (1962).
(22) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **85**, 3039 (1963); **86**, 1839 (1964).
(23) G. Losse, A. Barth, and K. Schatz, *Ann.*, **677**, 185 (1964).
(24) J. K. Sutherland and D. A. Widdowson, *J. Chem. Soc.*, 4651 (1964).
(25) S. Bittner, Y. Knobler, and M. Frankel, *Tetrahedron Letters*, 95 (1965).
(26) S. M. Beaumont, B. O. Handford, J. H. Jones, and G. T. Young, *Chem. Commun.* (London), 53 (1965).
(27) Unfortunately, this synthesis of activated esters derived from 1-hydroxy-2(1H)-pyridone requires an acid halide, itself an activated carboxyl function, as starting material. The alternate possibility of condensing the amino acid with 1-hydroxy-2(1H)-pyridone in the presence of a carbodiimide has not been studied by us; however, the success of

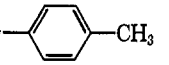
The Reaction of I with Sulfonyl Halides. The discovery of the interesting chemical properties of the 1-acyloxy-2(1H)-pyridones led us to investigate the related condensation of I with sulfonyl chlorides. The reaction also proceeds readily (the evolution of ethyl chloride begins on admixture of the two components)

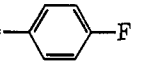


I XXII

a, R = CH_3

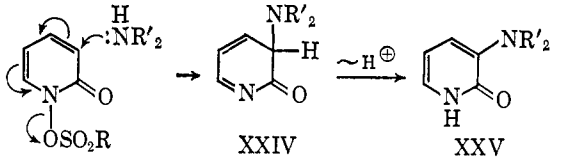
b, R = 

c, R = 

d, R = 

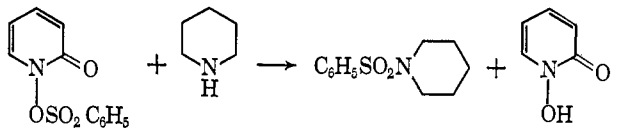
and furnishes the corresponding 1-sulfonyloxy-2(1H)-pyridones (XXII) in excellent yields. The sulfonate esters are highly crystalline and conveniently handled.

It appeared plausible that the sulfonate esters could react with a nucleophilic reagent (secondary amines were selected for the present study) in a variety of ways. For example, should the nucleophile attack at the 3-position, concomitantly with the appropriate migration of electrons (see XXIII), to eliminate the sulfonate group, the species XXIV would result and would rapidly tautomerize to XXV. Alternatively, it is conceivable that the amine could attack at the pyridone nitrogen atom to directly displace the sulfonate group and yield a 1-amino-2(1H)-pyridone. Attack at the



XXIII XXIV XXV

extranuclear sulfur atom is also possible, a process which would eventuate in the liberation of the 1-hydroxy-2(1H)-pyridone moiety and the formation of the corresponding sulfonamide. To differentiate between these possibilities, 1-hydroxy-2(1H)-pyridone benzenesulfonate (XXIIb) was treated with an excess of piperidine. A very exothermic reaction was observed from which a quantitative yield of 1-(phenylsulfonyl)piperidine was obtained. Identical results were obtained when pyrrolidine and morpholine were employed.



the latter method in related examples[21,22] would lead one to believe that the process is synthetically feasible.

(28) The lack of racemization in making a dipeptide unit is, unfortunately, not indicative of the optical stability which will result in attempts to prepare longer peptide chains. However, since active derivatives of phthaloyl amino acids racemize much more readily than the corresponding carbobenzoxy derivatives (B. Liberek, *Tetrahedron Letters*, 1103 (1963)), the reported example may prove a good test of optical stability.

Thus, the reaction may be interpreted reasonably as proceeding exclusively by a displacement reaction at tetravalent sulfur. Because such processes are relatively unfamiliar,[29] except in the case of activated sulfonic acid derivatives such as sulfonyl chlorides, these results suggest that the 1-sulfonyloxy-2(1H)-pyridones are activated in terms of the increased reactivity of S^{IV} in nucleophilic reactions.

The utility of compounds of the type XXII as replacements for the customarily employed sulfonyl halides in circumstances where the liberation of a hydrohalogen acid is undesirable awaits the test of experimentation.

Experimental Section[30]

1-Hydroxy-2(1H)-pyridone Acetate (II). With ice cooling, 21 g. (0.15 mole) of I was slowly added to 256 ml. of acetyl chloride and an instantaneous liberation of ethyl chloride was observed. The mixture was refluxed for 1 hr. on a steam bath and the excess acetyl chloride was evaporated under reduced pressure. The cooled residue crystallized on scratching. The solid was dissolved in ethyl acetate, and the cloudy solution was filtered and allowed to cool. The precipitated solid was filtered and dried to give 18.0 g. (85.7%) of white crystals, m.p. 88–90°. Pure pyridone was obtained as small white prisms from ethyl acetate, m.p. 93–94°, ν^{Nujol} 1800 and 1665 cm.$^{-1}$ (ester and amide carbonyls, respectively); λ_{max}^{EtOH} 228 mμ (ε 6850) and 302 mμ (ε 5500).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.84; H, 4.46; N, 9.03.

A slurry of 2.2 g. (0.02 mole) of III[31] in 15 ml. of acetic anhydride was warmed until solution was effected (*ca.* 10 min.). The excess acetic anhydride was evaporated *in vacuo* and the residual colorless oil was crystallized from ethyl acetate and dried to give 2.6 g. (96.4%) of II, m.p. 93–94°, whose infrared spectrum was identical with that of the sample prepared from I.

Aqueous Hydrolysis of II. A 1.4-g. (0.01 mole) sample of II was dissolved in 10 ml. of water. After 2 hr., colorless crystals began to deposit from solution. The solution was allowed to stand overnight at room temperature. The precipitated crystals were filtered and dried to give 1.1 g. (100%) of III as a white solid, m.p. 148–149°.

Reaction of II with n-Butylamine. To 1.5 g. (0.02 mole) of cold *n*-butylamine was added 2.8 g. (0.02 mole) of II. A strong exothermic reaction ensued, and as the reaction mixture began to cool, crystals began to deposit. After standing at room temperature for 1 hr., the solid was separated by filtration and washed thoroughly with an ether–hexane (1:1) mixture. The solid was recrystallized from ethyl acetate to give 1.5 g. (68.2%) of III, m.p. 147–148°. The filtrate was distilled to yield 1.7 g. (85%) of *n*-butylacetamide, b.p. 120–132° (13 mm.), identical by the usual criteria with an authentic sample.

(29) For a discussion of displacement reactions as tetravalent sulfur, see W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 64–70.

(30) All melting points are corrected. The microanalytical and spectral determinations were performed by the staff of the Physical and Analytical Chemistry Department of the Upjohn Co. under the direction of Dr. D. R. Myers.

(31) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

Reaction of II with n-Butyl Alcohol. A solution of 7.0 g. (0.05 mole) of II in 3.7 g. (0.05 mole) of *n*-butyl alcohol was warmed momentarily on a steam bath to initiate the reaction. Crystals soon began to appear and the mixture was allowed to stand at room temperature for 15 min. The solid was separated by filtration and was washed thoroughly with an ether–hexane (1:1) mixture. This solid was recrystallized from ethyl acetate to give 4.3 g. (78.2%) of III, m.p. 141–144°. The filtrate was distilled to give 2.3 g. of *n*-butyl acetate, b.p. 120–121°, identical by the usual criteria with an authentic sample.

Reaction of Benzoyl Halides with I. General Procedure A. Directly from the Acyl Halide. A mixture of 5.0 g. (0.036 mole) of I and 5.6 g. (0.04 mole) of benzoyl chloride was heated on a steam bath for 0.5–1 hr. The resulting solid was recrystallized from ethyl acetate to give 7.85 g. (92.4%) of white solid, m.p. 139–140°. Pure products were generally obtained after one or two additional recrystallizations from ethyl acetate.

General Procedure B. From the Carboxylic Acid. A quantity of benzoic acid, equimolar with the weight of I to be subsequently used, was refluxed with excess thionyl chloride for 1–2 hr. The excess thionyl chloride was evaporated under reduced pressure. A quantity of dry benzene was added and evaporated and the process was repeated a second time. The crude acid chloride was then treated with I as described above and the activated ester was isolated by the same procedure.

Phthaloyl-L-phenylalanylglycine Ethyl Ester (XXI). A mixture of 7.0 g. (0.05 mole) of I and 15.0 g. (0.05 mole) of phthaloyl-L-phenylalanyl chloride[32] was warmed on a steam bath for 0.5 hr. The resulting solid (18.6 g., 100%) was dissolved in 150 ml. of dry chloroform. To this stirred solution was added 7.0 g. (0.05 mole) of glycine ethyl ester hydrochloride. With external cooling to maintain the temperature at 20–25°, there was slowly added 5.0 g. (0.05 mole) of triethylamine. The solution was stirred for 15 min. at room temperature and washed with water, dilute hydrochloric acid, water, dilute sodium carbonate solution, and water. The organic layer was dried, filtered, and evaporated. The crystalline residue was recrystallized from ethanol to give 14.5 g. (79.7%) of white crystals, m.p. 158–159°, $[\alpha]^{29}D$ −145° (lit.[32] m.p. 160.6–161.4°, $[\alpha]^{29.5}D$ −146°).

Phthalylglycylglycine Methyl Ester (XIX). XIX was obtained by a similar procedure in 85.3% yield as white needles from water, m.p. 200–201° (lit.[32] m.p. 203–204°).

1-Hydroxy-2(1H)-pyridone Methanesulfonate (XXIIa). A mixture of 5.0 g. (0.036 mole) of I and 4.6 g. (0.04 mole) of methanesulfonyl chloride was heated on a steam bath for 1 hr. The evolution of ethyl chloride began immediately. On cooling and scratching, the oil crystallized. Recrystallization of this material from ethyl acetate gave 5.9 g. (86.8%) of product, m.p. 71–76°. Pure XXIIa was obtained as large, white prisms from ethyl acetate, m.p. 77–79°, ν^{Nujol} 1673 cm.$^{-1}$ (pyridone carbonyl), λ_{max}^{EtOH} 226 mμ (ε 4250) and 298 mμ (ε 5250).

Anal. Calcd. for $C_6H_7NO_4S$: C, 38.09; H, 3.73; N, 7.40; S, 16.95. Found: C, 38.01; H, 3.60; N, 7.31; S, 16.84.

1-Hydroxy-2(1H)-pyridone Benzenesulfonate (XXIIb). XXIIb was obtained by a similar procedure in 90.0% yield after one recrystallization, as small white prisms from ethyl acetate: m.p. 135.5–137°; ν^{Nujol} 1690 cm.$^{-1}$ (pyridone carbonyl); λ_{max}^{EtOH} 223 (15,150), 261 sh (2200), 270 sh (3050), 276 (3500), and 301 (4950) mμ.

Anal. Calcd. for $C_{11}H_9NO_4S$: C, 52.58; H, 3.61; N, 5.57; S, 12.76. Found: C, 52.57; H, 3.43; N, 5.59; S, 12.52.

1-Hydroxy-2(1H)-pyridone p-Toluenesulfonate (XXIIc). XXIIc was obtained by a similar procedure in 86.8% yield after one recrystallization as white prisms from ethyl acetate: m.p. 101–102.5°; ν^{Nujol} 1684 cm.$^{-1}$ (pyridone carbonyl); λ_{max}^{EtOH} 229 (17,300), 270 sh (2700), 278 sh (3200), 301 (4900), and 324 sh (2500) mμ.

Anal. Calcd. for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.67; H, 4.43; N, 5.12; S, 11.73.

1-Hydroxy-2(1H)-pyridone p-Fluorobenzenesulfonate (XXIId). XXIId was obtained by a similar procedure in 76.2% yield after one recrystallization as white prisms from ethyl acetate: m.p. 130–132°; ν^{Nujol} 1682 cm.$^{-1}$ (pyridone carbonyl); λ_{max}^{EtOH} 224 (14,650), 261 sh (1350), and 301 (4650) mμ.

Anal. Calcd. for $C_{11}H_8FNO_4$: C, 49.06; H, 2.99; N, 5.20; S, 11.91. Found: C, 49.23; H, 3.03; N, 5.04; S, 12.03.

4-(Phenylsulfonyl)morpholine. A 15.0-g. (0.06-mole) sample of XXIIb was gradually added in small portions to 17.4 g. (0.20 mole) of morpholine. The reaction was very exothermic. After standing at room temperature for 4 hr., the reaction mixture was treated with 100 ml. of methylene chloride and 25 ml. of water. The organic layer was separated, dried, filtered, and evaporated to give 13.5 g. (99.3%) of pale yellow solid, m.p. 116–117°. Recrystallization of this material from ethyl acetate–hexane gave white needles, m.p. 117–118° (lit.[33] m.p. 118°). This material was identical by the usual criteria with an authentic sample.

In a similar manner, 1-(phenylsulfonyl)pyrrolidine, white crystals from ethyl acetate–hexane, m.p. 51.5–52°,[34] and 1-(phenylsulfonyl)piperidine, white needles from ethyl acetate–hexane, m.p. 92–93°, could be obtained in yields of 81 and 100%, respectively.

(32) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, 74, 3822 (1952).

(33) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 234.

(34) R. F. Brown and N. M. VanGulick, *J. Am. Chem. Soc.*, 77, 1079 (1955), report m.p. 51.5–52.0° for this material.