

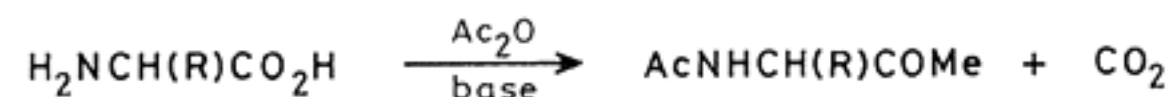
The Dakin–West Reaction

By G. L. Buchanan

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF GLASGOW,
GLASGOW G12 8QQ

1 Introduction

The direct conversion of an α -amino-acid into the corresponding α -acetyl-amino-alkyl methyl ketone by the action of acetic anhydride in the presence of a base such as pyridine, takes place with the evolution of CO_2 and is generally known as the Dakin–West reaction (Scheme 1).¹ Its discovery by these two authors in 1928 was accompanied by a brief exploration of its nature, its scope, and its mechanism.² A little earlier, others³ had observed that both tyrosine and α -phenylalanine afforded 'abnormal' products when acetylated under these conditions. However, they were slow to identify the products⁴ and the reaction is invariably credited to Dakin and West.



Scheme 1

Most general references¹ to the reaction describe only the conversion of an α -primary amino-acid, as in the above example. But, in fact, non-amino-acids such as phenylacetic acid also yield methyl ketones under these conditions, as do secondary amino-acids, which Dakin and West believed to be constitutionally incapable of undergoing this transformation.² More recent work has also improved the efficiency of many of these conversions and this simple 'one-pot' conversion of a carboxylic acid into a ketone, under mild conditions, often proceeds in good yield. It deserves to be better known.

These transformations do not all involve the same reaction mechanism, but they all involve the same reaction conditions and, for the purpose of this review, they are all included as examples of the general Dakin–West reaction. This review discusses these reaction mechanisms but it deals particularly with the preparative scope and efficiency of the reactions. Experimental details and yields are summarized in the Tables (pp. 000—000).

¹ Merck Index 10th Edn., ONR-22, Merck & Co. Inc., USA, 1983; H.O. House 'Modern Synthetic Reactions', 2nd Edn. W. A. Benjamin Inc., 1972, pp. 770—773; 'Comprehensive Organic Chemistry', ed. D. H. R. Barton and W. D. Ollis, Vol. 2, Pergamon Press, Oxford 1979, p. 828.

² H. D. Dakin and R. West, *J. Biol. Chem.*, 1928, **78**, 91, 745, and 757.

³ P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, 1927, **74**, 689.

⁴ P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, 1928, **79**, 95.


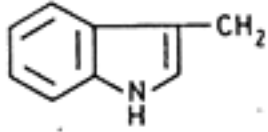

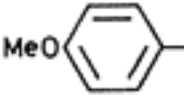
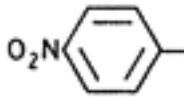
2 Primary α -Amino-acids

In the original investigations² in which acetic anhydride was allowed to react with, *inter alia*, phenylalanine, tyrosine, leucine, alanine, and 2-phenylglycine, in the presence of pyridine at steam-bath temperature, it was noted that CO₂ was evolved and that a base was essential. It was shown also that pyridine could be replaced by alkylpyridines^{2,5} or sodium acetate⁶ but not by quinoline or *N,N*-dimethylaniline. Whilst amino-acids yield ketones under these conditions, the related amines such as benzylamine are merely *N*-acetylated. No reaction was observed with β -amino-acids or with α -amino-acids which lacked one C(2)-H; *e.g.* α -aminohydratropic acid (1).² At these temperatures (*ca.* 100 °C) no reaction took place with secondary amino-acids, *e.g.* sarcosine (2) or proline (3) or with the tertiary amino-acid (4);² however, they *do* react at reflux temperature (see Section 3). Acetic anhydride may be replaced by other anhydrides affording for example ethyl- or propyl-ketones in good yields, particularly under modified reaction conditions⁵⁻⁷ but, in general, yields diminish with increasing chain length in the acid anhydride. Benzoic

Table 1 α -Amino-acids

$\begin{array}{c} R^2 \\ \\ R^1NHCHCO_2H \end{array} \xrightarrow[\text{base}]{(R^3CO)_2O} \begin{array}{c} R^2 \\ \\ R^1NHCHCOR^3 \end{array}$		Reaction Conditions	Yield %	Ref.
H	H	Me	py; reflux; 6 h; H ₂ O	60 R ¹ = Ac <i>a</i>
PhCO	H	Me	3-pic; r.t.; 2 h; H ₂ O	77 <i>b</i>
PhCO	H	Et	3-pic; r.t.; 2 h; H ₂ O	73 <i>b, c</i>
PhCO	H	Pr ⁿ	2-pic; 35 °C; 3 h; H ₂ O	71 <i>c</i>
PhCO	H	F ₃ C	10–15 °C; 17 h; H ₂ O	75 <i>d</i>
PhCO	H	F ₅ C ₂	10–15 °C; 17 h; H ₂ O	34 <i>d</i>
PhCO	H	F ₇ C ₃	10–15 °C; 17 h; H ₂ O	54 <i>d</i>
H	Me	Me	py; 100 °C; 6 h; stir	81–88 R ¹ = Ac <i>e</i>
PhCO	Me	Me	Et ₃ N; DMAP; ½ h; r.t.	78 <i>f</i>

Table 1 α -Amino-acids (continued)

R ¹	R ²	R ³	Reaction Conditions	Yield %	Ref.
H	Me	Ph	py; 135 °C; 2½ h; stir	42 R ¹ = PhCO	<i>g</i>
H	Me ₂ CHCH ₂	Me	py; 100 °C; 6 h	70 R ¹ = Ac	<i>h</i>
H	Ph	Me	py; 100 °C; 5½ h	72 R ¹ = Ac	<i>h</i>
H	Ph	Et	py; reflux; 1½ h	75 R ¹ = EtCO	<i>a</i>
	Ph	Me	py; DMAP; 25 °C; stir 20 min	82	<i>i</i>
H	PhCH ₂	Me	py; 100 °C; 5 h	79 R ¹ = Ac	<i>g</i>
H	PhCH ₂	Et	py; 135 °C; 1½ h	41 R ¹ = EtCO	<i>g</i>
H	PhCH ₂	Pr ⁿ	py; 135 °C; 3 h	27 R ¹ = PrCO	<i>g</i>
H	PhCH ₂	MeOCH ₂	py; 115 °C; 1 h; stir	78 R ¹ = MeOCH ₂ CO (crude)	<i>g</i>
H	PhCH ₂	Ph	py; 145 °C; 2 h	44 R ¹ = PhCO	<i>g</i>
H		Me	Et ₃ N; DMAP; 20 min; stir	75 R ¹ = Ac	<i>i</i>
	MeSCH ₂ CH ₂	Me	py; DMAP; EtOAc; reflux; 2 h	67	<i>i</i>
Ph	H	Me	reflux; 6 h	67 ^g	<i>j</i>
Ph	H	Et	reflux; 4 h	55 ^r	<i>j</i>
	H	Me	reflux; 1 h	45 ^g	<i>j</i>
	H	Me	reflux; 1 h	22 ^g	<i>j</i>
Ph	Me	Me	py; reflux; 1 h	13 ^g	<i>j</i>
Me	Me ₂ CHCH ₂	Me	4-pic; 130 °C; 10 h	36 ^g	<i>k</i>
Me	Me ₂ CH	Me	py; 140 °C; 8 h	37 ^g	<i>k</i>
PhCO	CH ₂ CH ₂ CO ₂ H	Me	py; 110 °C; 45 min	90 ⁿ	<i>l</i>
PhCO	CH ₂ CH ₂ CO ₂ H	Et	py; reflux; 45 min	75 ⁿ	<i>l</i>
PhCO	CH ₂ CH ₂ CO ₂ H	Pr ⁿ	2-pic; 110 °C; 1 h	31 ⁿ	<i>l</i>
PhCO	CH ₂ CH ₂ CO ₂ H	C ₅ H ₁₁	2-pic; 120 °C; 2 h	30 ⁿ	<i>l</i>
PhCO	CH ₂ CH ₂ CO ₂ H	Ph	2-pic; 100 °C; 1 h	26 ⁿ	<i>l</i>
H	CH ₂ CH ₂ CO ₂ H	Me	Et ₃ N; DMAP; 60 °C; 8 h	76 ^p	<i>m</i>

^a R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, 1948, **70**, 2005; ^b ref. 5; ^c R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 1952, 1350; ^d E. J. Bourne, J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow, *J. Chem. Soc.*, 1961, 1771; ^e ref. 7; ^f ref. 16; ^g ref. 6; ^h ref. 63; ⁱ ref. 21; ^j ref. 34; ^k ref. 32; ^l ref. 15; ^m ref. 62;

ⁿ R³CO-N(COPh)₂; ^p R³CO-N(Ac)₂; ^q NAc derivative; ^r NCO-Et derivative.

⁵ J. Attenburrow, D. F. Elliot, and G. F. Penny, *J. Chem. Soc.*, 1948, 310.

⁶ G. H. Cleland and C. Nieman, *J. Am. Chem. Soc.*, 1949, **71**, 841.

⁷ R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, 1948, **70**, 2005; *Org. Synth. Coll.*, Vol IV, 5, (1963).

Table 2 Other Acids

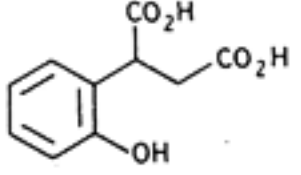
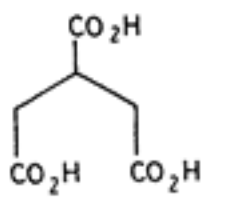
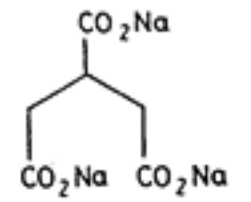
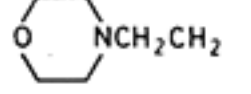
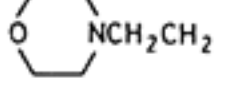
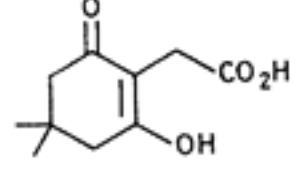
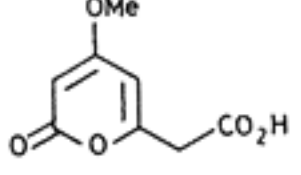

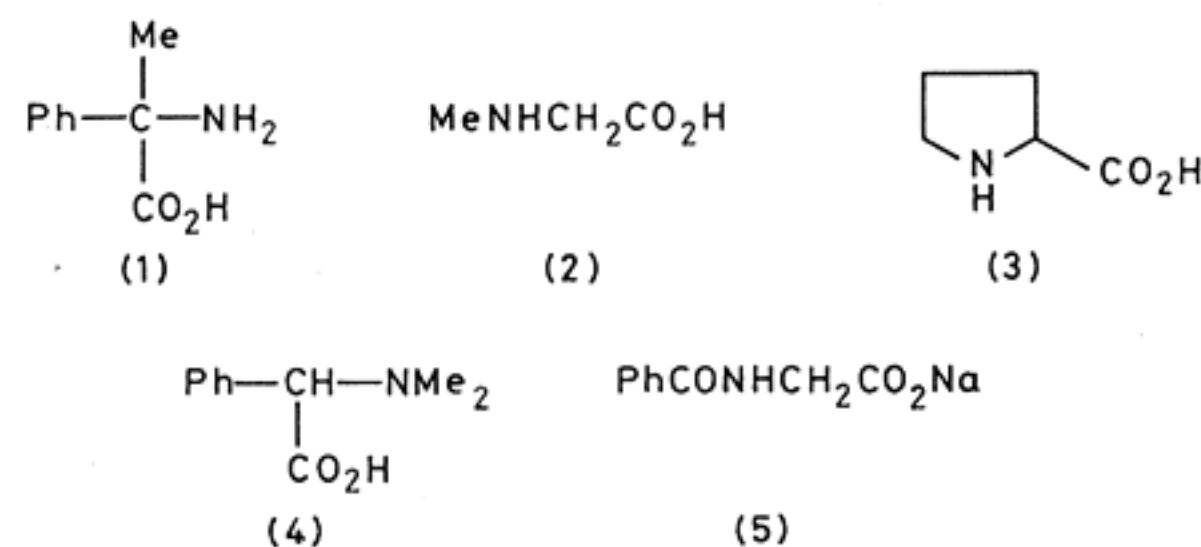
$R^1 R^2 CHCO_2H$		$(R^3CO)_2O$ base	$R^1 R^2 CHCOR^3$	Reaction Conditions	Yield %	Ref.
R^1	R^2	R^3				
H	Ph	Me		py; reflux; 6 h	56 + 24 ^a	<i>h</i>
H	Ph	Me		py; 120 °C; 67 h; stir	28 + 33 ^b	<i>i</i>
H	Ph	Et		py; 120 °C; 42 h; stir	50 + 16 ^b	<i>i</i>
H	Ph	Pr		py; 120 °C; 31 h; stir	38 + 18 ^b	<i>i</i>
H		Me		py; 120 °C; 4 h; stir	48 ^b	<i>i</i>
Me	6-purinyI-thio	Me		reflux; 5 h	57 ^c	<i>j</i>
Me	6-purinyI-thio	Et		reflux; 6 h	44 ^c	<i>j</i>
H	PhS	Me		2,6-lutid; reflux; 12 h	21	<i>j</i>
H	PhO	Me		py; reflux; 12 h; stir	17	<i>j</i>
H	3-pyridyl	Me		NaOAc; reflux; 17 h	39	<i>k</i>
		Me		reflux; 1 h	100 ^{d,e}	<i>l</i>
		Et		reflux; 1 h	72 ^{d,e}	<i>l</i>
		Pr ⁿ		reflux; 1 h	67 ^{d,e}	<i>l</i>
		Me		reflux; 2 h	84 ^f	<i>l</i>
		Ph		reflux; 2 h	13 ^f	<i>l</i>
		n-C ₈ H ₁₇		glass powder; 185 °C; 7 h/N ₂	49 ^f	<i>m</i>
		Me		125 °C; 36 h	42 ^f	<i>n</i>
		Et		125 °C; 36 h	20 ^f	<i>n</i>
		Pr ⁿ		125 °C; 36 h	17 ^f	<i>n</i>
		Pr ⁱ		125 °C; 36 h	9 ^f	<i>n</i>
		Ph		125 °C; 48 h	5 ^f	<i>n</i>
H		Me		reflux; 15 min/N ₂	58	<i>p</i>
H		Et		reflux; 15 min/N ₂	57	<i>p</i>
H	Et ₂ NCH ₂ CH ₂	Me		reflux; 15 min/N ₂	47	<i>p</i>
H	Pr ⁱ ₂ NCH ₂ CH ₂	Me		reflux; 15 min/N ₂	66	<i>p</i>
		Me		NaOAc; 125 °C; 35 min	48 ^g	<i>q</i>
		Me		py; r.t.; 4 h	45	<i>r</i>

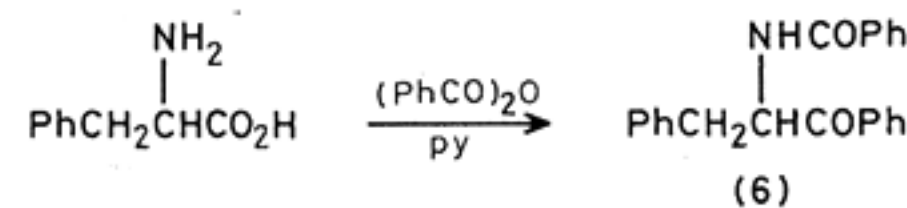
Table 2 Other Acids (continued)

R^1	R^2	R^3	Reaction Conditions	Yield %	Ref.
		Me	pyr; reflux; 35 h	73	<i>s</i>

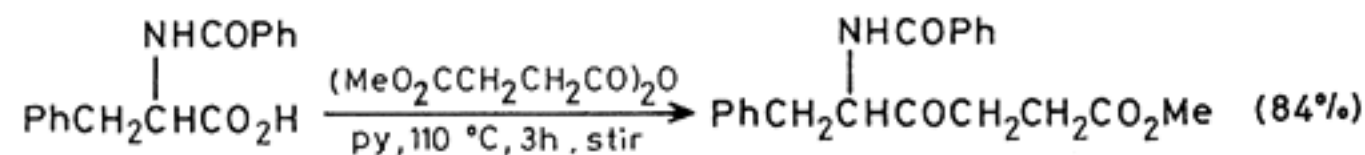
^a Ketonic by-product, $R^3 = PhCH_2$; ^b enol-ester; ^c *N*-acyl derivative; ^d crude; ^e cf. structure (48); ^f structure (52); ^g keto-lactone; ^h ref. 45; ⁱ ref. 46; ^j ref. 52; ^k ref. 56; ^l ref. 13b; ^m ref. 56; ⁿ ref. 55; ^p ref. 57; ^q ref. 65; ^r ref. 53; ^s ref. 48.



anhydride gives moderate yields of the phenylketone (6),⁶ but neither phthalic anhydride nor succinic anhydride produces any ketone from phenylalanine. However, the bimolecular anhydride-ester derived from succinic acid behaves normally affording keto-ester in 84% yield (Scheme 3).⁸



Scheme 2



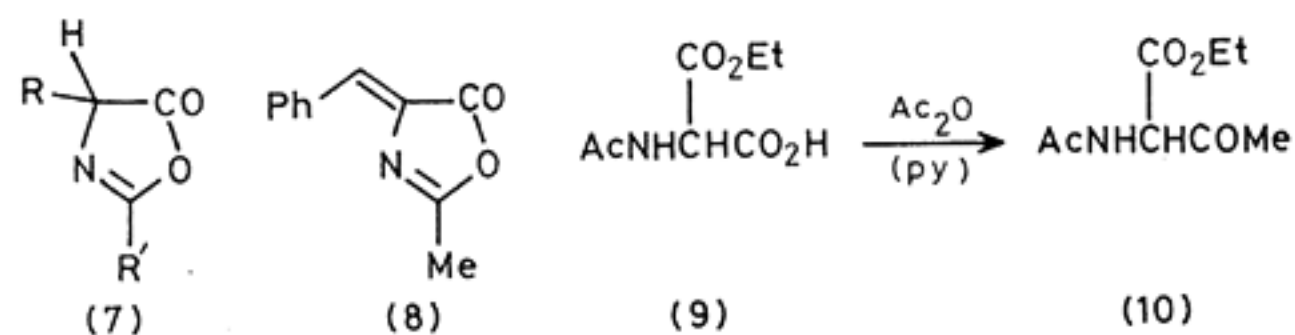
Scheme 3

The use of higher reaction temperatures (*e.g.* 120 °C) and mechanical stirring⁷ also improve the yields obtained with acetic anhydride. In the case of glycine, whose conversion into α -acetylaminoacetone under original (steam-bath) conditions was inexplicably poor, these modifications raise it to *ca.* 60%. Even better results have been obtained by employing sodium hippurate (5) in place of glycine.^{5,9} Dakin and West also observed² that 'saturated' oxazol-5-ones (7) yield the same product as

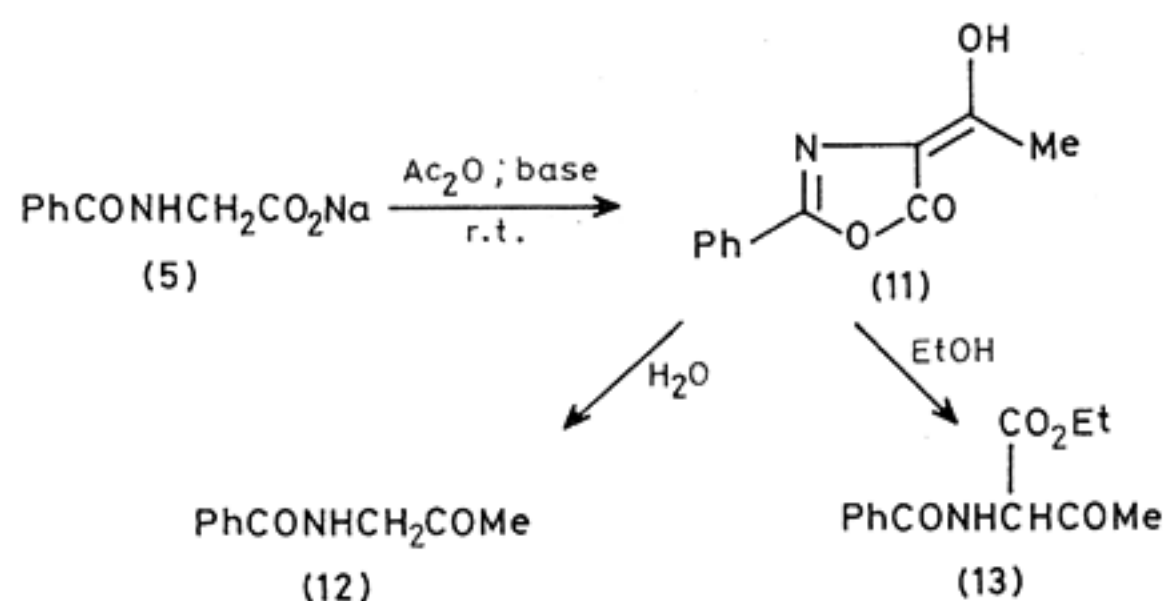
⁸ G. H. Cleland and F. S. Bennett, *Synthesis*, 1985, 681.

⁹ (a) R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 1952, 1350; (b) E. J. Bourne, J. Burdon, V. C. R. McLoughlin, and J. C. Tatlow, *J. Chem. Soc.*, 1961, 1771.

the parent amino-acid and concluded that they might be reaction intermediates. On the other hand, the β -hydroxyamino-acid phenylserine undergoes dehydration and the reaction stops at the 'unsaturated' oxazolone (8).² 'Unsaturated' oxazolones are unaffected by acetic anhydride and pyridine.



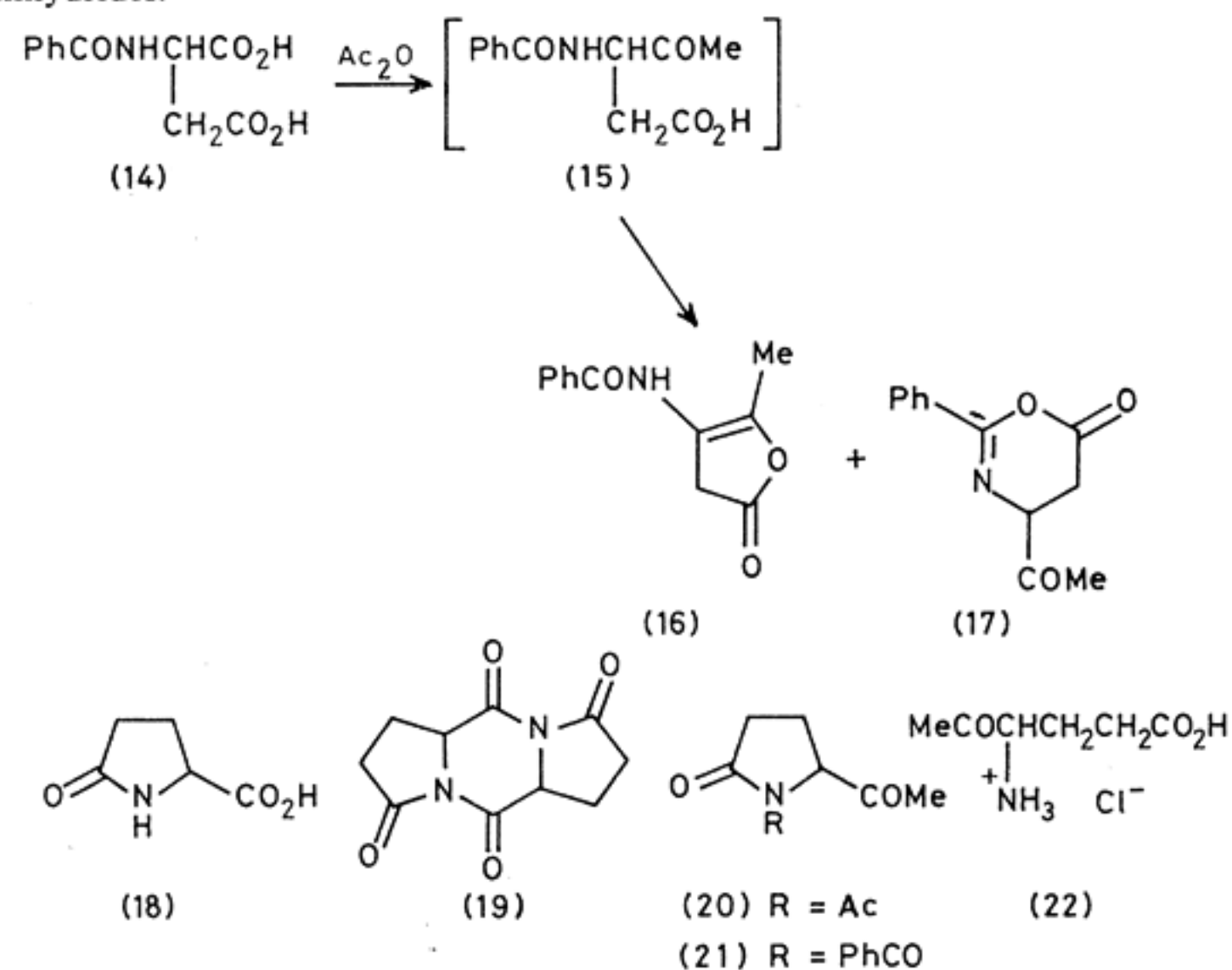
If the reactivity of the α -CH is enhanced by an additional electrophilic group, as in the malonic half-ester (9), the conversion into ketone (10) takes place under milder conditions *viz.*, overnight at room temperature¹⁰ or under reflux with acetic anhydride alone.¹¹ Another example is provided by 2-phenylglycine.¹² Higher yields are claimed⁹ when the amino-acid is first converted into its *N*-benzoyl derivative and used as its sodium salt. This technique, which was first introduced by Attenburrow, Elliot, and Penny,⁵ affords the acyloxazolone (11) at room temperature, and from it (12), in much higher yield than by the direct Dakin-West reaction on glycine (Scheme 4). Alternatively, ethanolysis of the intermediate leads directly to the β -ketoester (13).⁵ It is even claimed that *all* α -benzamido-acids will undergo (slow) decarboxylative acylation by anhydrides without the need to add a base.¹³



Scheme 4

When the Dakin-West reaction is applied to α -aminodicarboxylic acids, special problems arise. Thus, under standard conditions aspartic acid yields only impure ketonic material.² But its *N*-benzoyl derivative (14) reacts with a variety of

anhydrides, even in the absence of added base, to give lactones of type (16) and/or (17), presumably *via* the ketone (15) (Scheme 5).^{11,13,62} Likewise, glutamic acid, which yields a mixture of products [(18)—(20)] under Dakin-West conditions,^{2,14} responds to the Attenburrow modification, affording (21) and thence (22).¹⁵ Homologous ketoacids have also been prepared by this route from the appropriate anhydrides.¹⁵



Scheme 5

More recent developments have revealed that, when a trace of 4-dimethylamino-pyridine (DMAP) is added to the reaction mixture, the Dakin-West reaction can be carried out at or near room temperature, and more rapidly than under standard reaction conditions (Scheme 6).^{16,17} Even so, it is wasteful to use an anhydride as the acylating agent in cases where the corresponding acid is scarce, for only half of the reagent is utilized. Steglich and Höfle have overcome this objection by using the acid chloride (despite several reported failures^{2,5,6}) in a 'stepwise procedure' (Scheme 7).^{18,19} This uses a preformed oxazolone, *e.g.* (23), which is *O*-acylated by the acid chloride in the presence of Et_3N then rearranged by DMAP²⁰ to the

¹⁴ J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 1952, **74**, 2859.

¹⁵ R. A. F. Bullerwell, A. Lawson, and H. V. Morley, *J. Chem. Soc.*, 1954, 3283.

¹⁶ W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 981.

¹⁷ G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 576.

¹⁸ W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 61.

¹⁹ W. Steglich and G. Höfle, *Chem. Ber.*, 1969, **102**, 883.

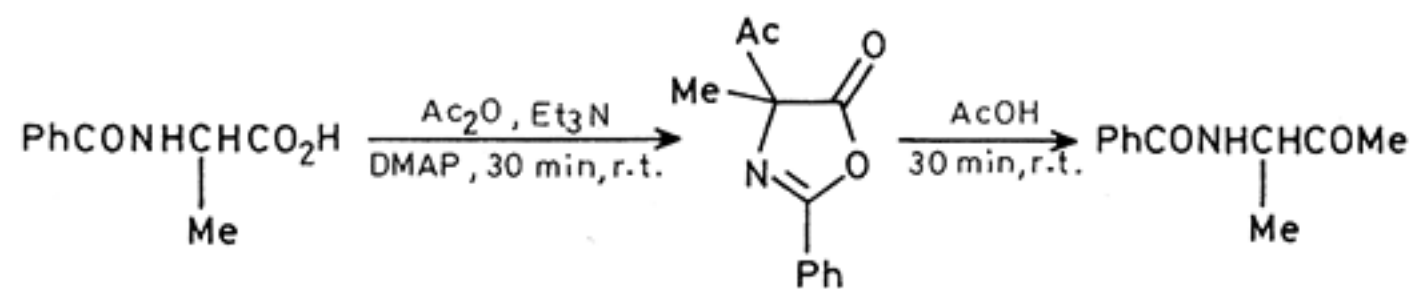
²⁰ W. Steglich and G. Höfle, *Tetrahedron Lett.*, 1970, 4727.

¹⁰ N. F. Albertson, B. F. Tuller, J. A. King, B. B. Fishburn, and S. Archer, *J. Am. Chem. Soc.*, 1948, **70**, 1150.

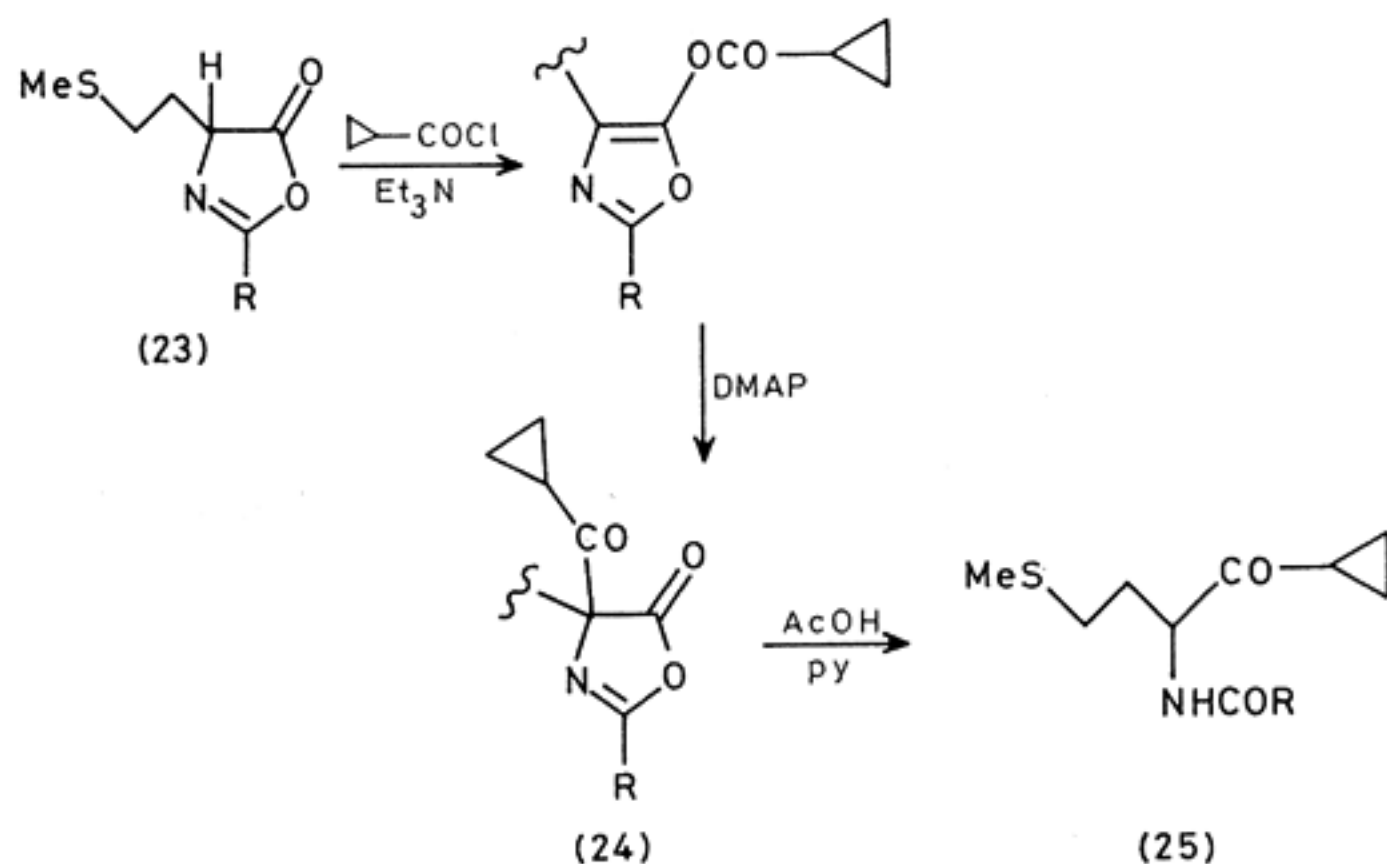
¹¹ A. Lawson, *J. Chem. Soc.*, 1953, 1046.

¹² J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 1955, **77**, 2814.

¹³ (a) A. Lawson, *J. Chem. Soc.*, 1954, 3363; (b) *ibid.*, 1957, 144.

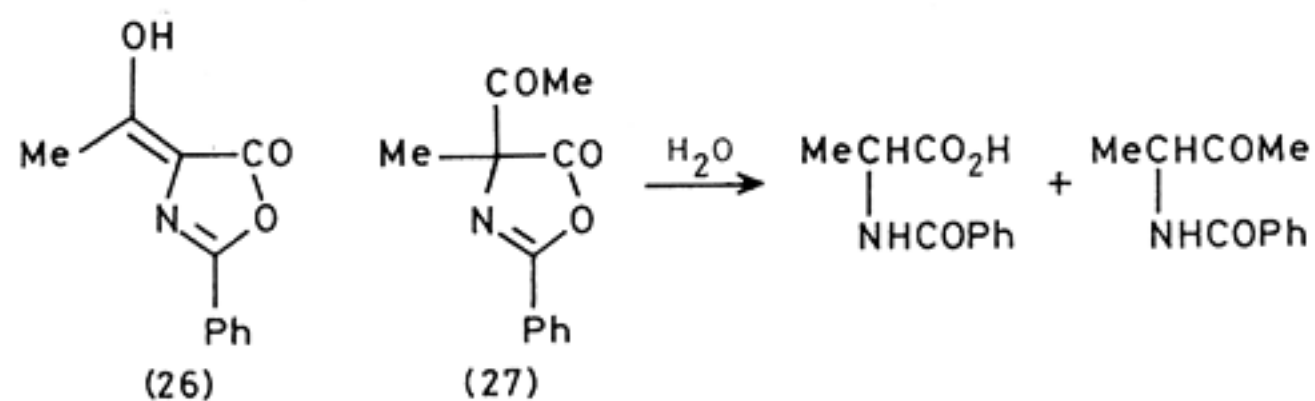


Scheme 6

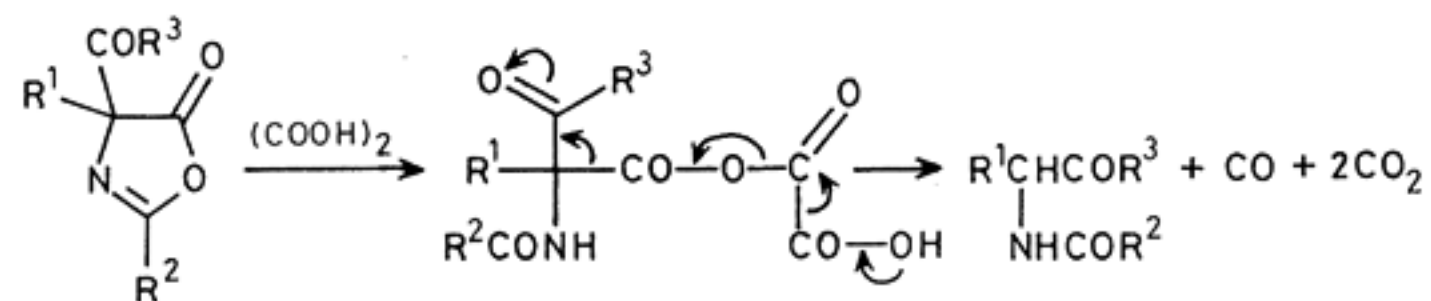


Scheme 7

thermodynamically preferred *C*-acyl derivative (24) and finally decomposed with loss of CO_2 to the ketone (25) ($\text{R} = 4\text{-ClPh}$).²¹ The overall yield in this case is 85%. Both routes lead to high yield conversions under mild reaction conditions and are therefore applicable to sensitive molecules.^{18,22} In the stepwise route, ring-opening and decarboxylation, (24) \rightarrow (25), are usually achieved by adding acetic acid and pyridine but also occur readily on boiling with water, provided the acylated oxazolone is enolizable, as in (26).^{5,19} However, 4-substituted-4-acyloxazolones such as (27) are open to attack at both carbonyl centres and yield mixtures



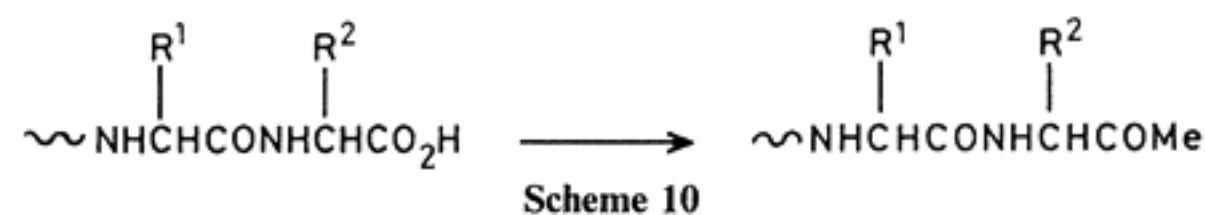
Scheme 8



Scheme 9

(Scheme 8).¹⁹ This undesirable side-reaction has been avoided by the use of acetic anhydride and pyridine or by reaction with anhydrous oxalic acid¹⁹ as shown in Scheme 9.

Under standard Dakin-West conditions the terminal CO_2H of a peptide is selectively converted into methyl ketone and, if the mild reaction conditions of the DMAP-catalysed reaction are employed, sensitive protecting groups remain undamaged.²² This conversion has been used to identify the *C*-terminal amino-acid of peptides by comparing (paper chromatography) the amino-acid content of the hydrolysate before and after reaction (Scheme 10). The method is applicable to 5–10 mg samples of peptide.²³



Scheme 10

The mechanism which Dakin and West themselves proposed² for the reaction of primary amino-acids involved *N*-acylation followed by a *C*-acylation and finally decarboxylation of the β -keto-acid. Others invoked the oxazolone as an intermediate with its stabilized carbanion,^{5,6} and later studies have only confirmed and added detail to this framework. These and other mechanistic studies have been reviewed by Allinger²⁴ who has set out the accepted mechanism in detail. It can be summarized as in Scheme 11.

It is consistent with this mechanism that α -amino-acids lacking a $\text{C}(2)\text{-H}$ do not react to produce a ketone,² that intermediate *C*-acylated oxazolones have been isolated from the reaction and shown to be ketone precursors,^{5,25,26} and that alanine labelled with ^{14}C at $\text{C}(1)$ gave rise to labelled CO_2 plus unlabelled ketone.²⁷

In a detailed examination of the acylation step (Scheme 12), Steglich and Höfle^{20,28,29} have shown the acylation of the oxazolone by acetic anhydride-pyridine mixtures involves a hitherto unsuspected intermediate (28) whose initial appearance and subsequent decay, with concomitant emergence of (29), has been followed by n.m.r. On the other hand, acylation by means of an acyl halide in the

²³ R. A. Turner and G. Schmerzler, *J. Am. Chem. Soc.*, 1954, **76**, 949.

²⁴ N. L. Allinger, G. L. Wang, and B. B. Dewhurst, *J. Org. Chem.*, 1974, **39**, 1730.

²⁵ P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *J. Am. Chem. Soc.*, 1956, **78**, 3503.

²⁶ Y. Iwakura, F. Toda, and H. Suzuki, *J. Org. Chem.*, 1967, **32**, 440.

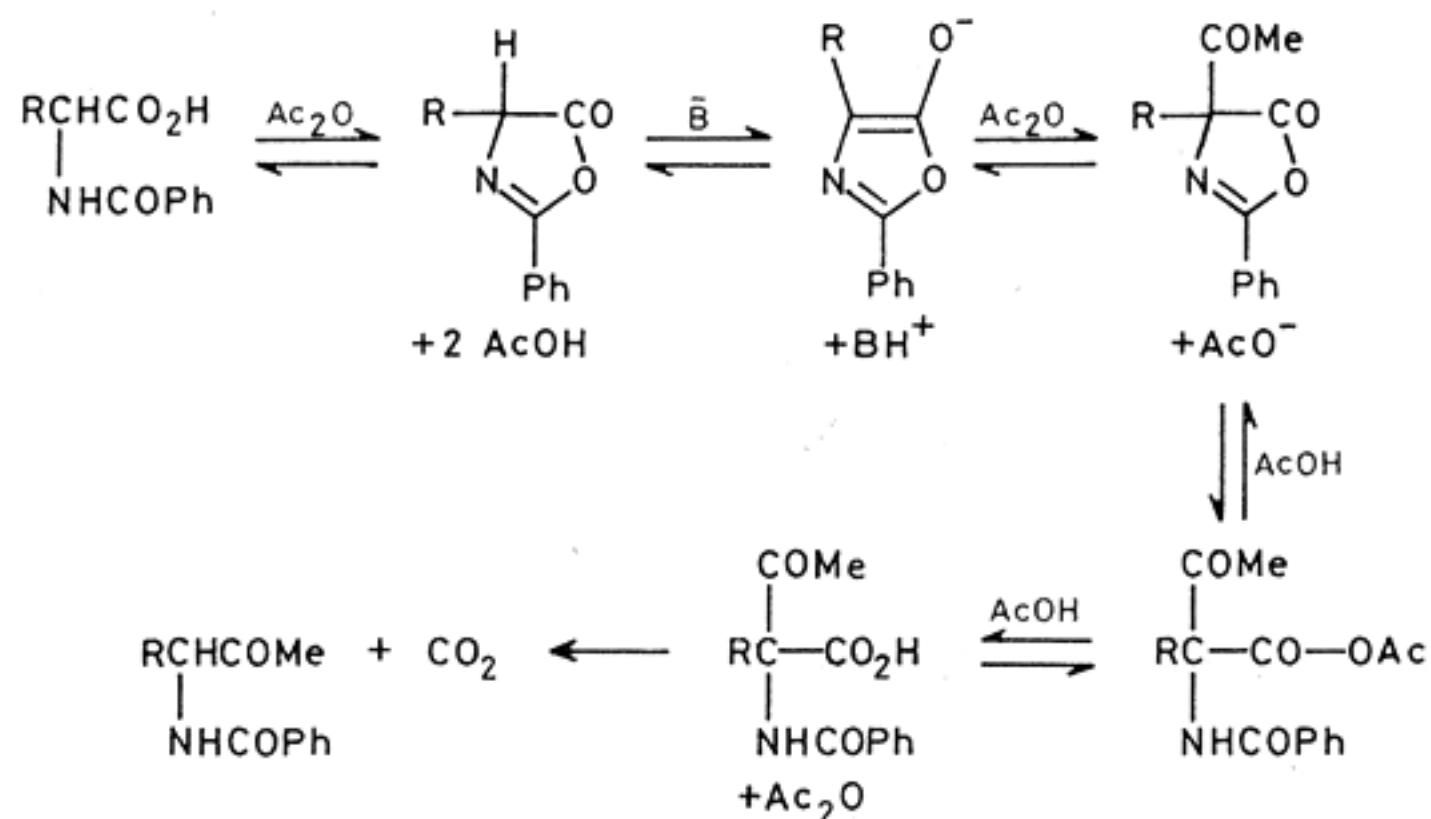
²⁷ C. S. Rondestvedt, jun., B. Manning, and S. Tabiban, *J. Am. Chem. Soc.*, 1950, **72**, 3183.

²⁸ W. Steglich and G. Höfle, *Tetrahedron Lett.*, 1968, 1619.

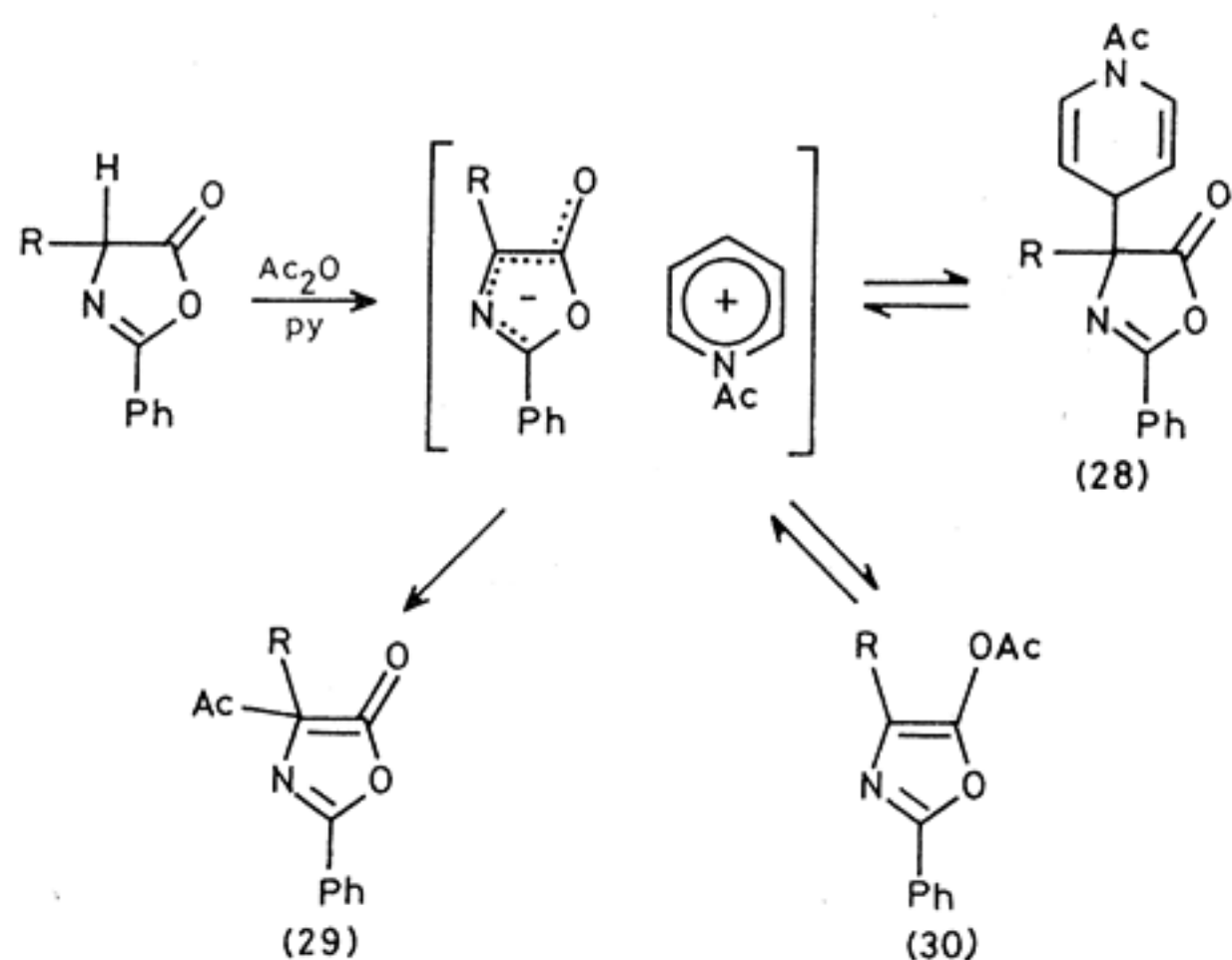
²⁹ W. Steglich and G. Höfle, *Chem. Ber.*, 1971, **104**, 3644.

²¹ N. Engel and W. Steglich, *Liebigs Ann. Chem.*, 1978, 1916.

²² J. S. McMurray and D. F. Dykes, *J. Org. Chem.*, 1985, **50**, 1112.



Scheme 11

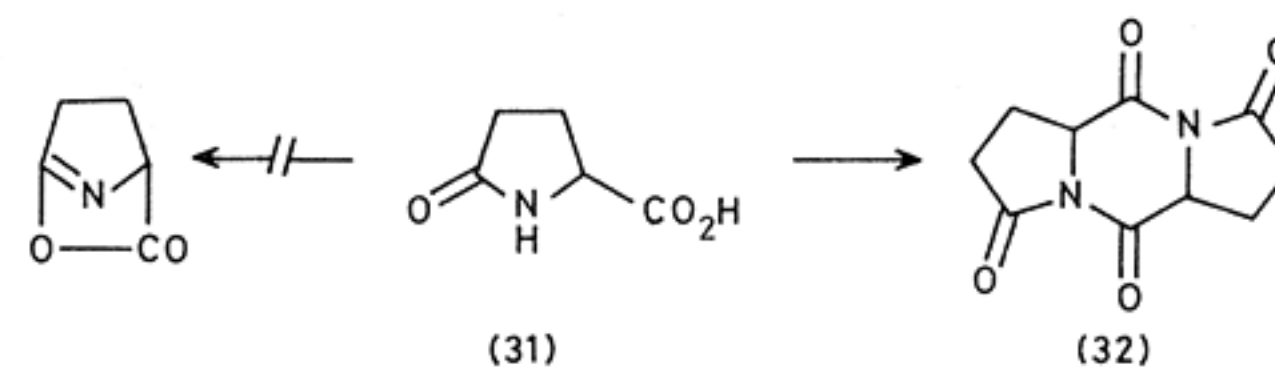


Scheme 12

presence of Et_3N gives rise to a mixture of (29) and (30) in which the acyloxazolone (30) can be isomerized to (29) by pyridine.^{18,19}

The same authors have shown that the attack of acetic acid on the acyloxazolone (29) occurs exclusively at C(5); alternative reaction at C(2) was ruled out by ^{18}O studies.³⁰

³⁰ G. Höfle, A. Prox, and W. Steglich, *Chem. Ber.*, 1972, **105**, 1718.

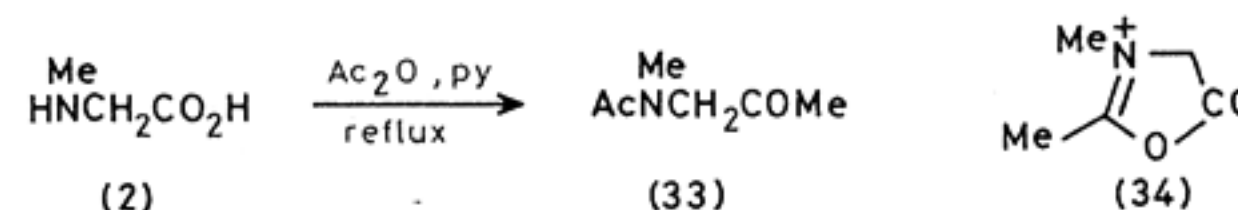


Scheme 13

It is of interest to note (Scheme 13) that in the case of 2-pyrrolidone-5-carboxylic acid (31), where oxazolone formation is forbidden by Bredt's Rule, no decarboxylation occurs¹⁴ and the reaction takes a new course leading to the dimer (32); *i.e.* acylation *via* a simple Claisen-type mechanism is not observed.

3 Secondary α -Amino-acids

The initial report² that secondary amino-acids are *not* converted into ketones under Dakin-West conditions seemed to confirm the view that oxazolone formation was an essential first step in the mechanism of the Dakin-West reaction. However, the report was mistaken because, at slightly higher temperatures, sarcosine (2) gives a moderate yield of methyl ketone (33),³¹ and *N*-methyl valine and *N*-methyl leucine were likewise found to undergo decarboxylative acylation in modest yield (Scheme 14).³²



Scheme 14

To accommodate these developments, Cornforth and Elliott proposed³³ that in secondary amino-acids the mechanism involves an oxazolinium intermediate (34). Other postulated mechanisms have not survived criticism.²⁴ Significantly, *N*-methyl-2-pyrrolidone-5-carboxylic acid, which is not capable of forming the oxazolinium intermediate (35) (Bredt's rule), is returned unchanged even under forced conditions.²⁴ This experiment excludes the alternative of a Claisen-type mechanism which has been given consideration.³⁴ On the other hand, no ketonic products have ever been obtained from proline (3)^{2,14,35} or from *N*-formyl-*N*-phenylglycine (36),³⁴ although the former at least has been shown to be capable of forming an oxazolinium ion intermediate with acetic anhydride.³⁶ Both were

³¹ R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, 1950, **72**, 1626.

³² R. Hinderling, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 1955, **38**, 1415.

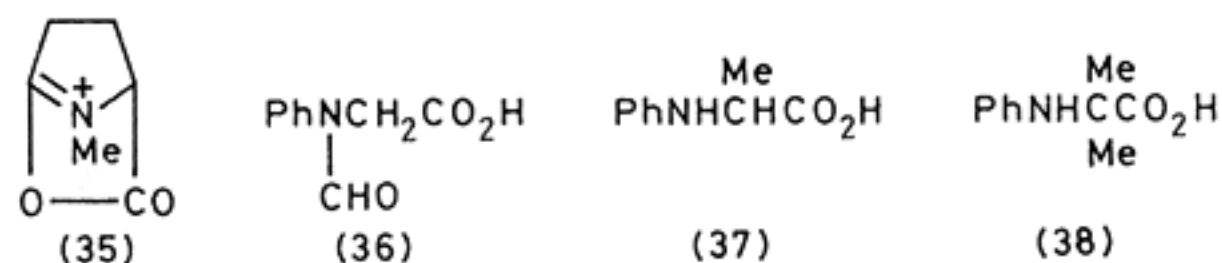
³³ J. W. Cornforth and D. F. Elliott, *Science*, 1950, **112**, 534.

³⁴ G. L. Buchanan, S. T. Reid, R. E. S. Thomson, and E. G. Wood, *J. Chem. Soc.*, 1957, 4227.

³⁵ Z. H. Israili and E. E. Smismann, *J. Chem. Eng. Data*, 1977, **22**, 357.

³⁶ R. Huisgen, G. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 136.

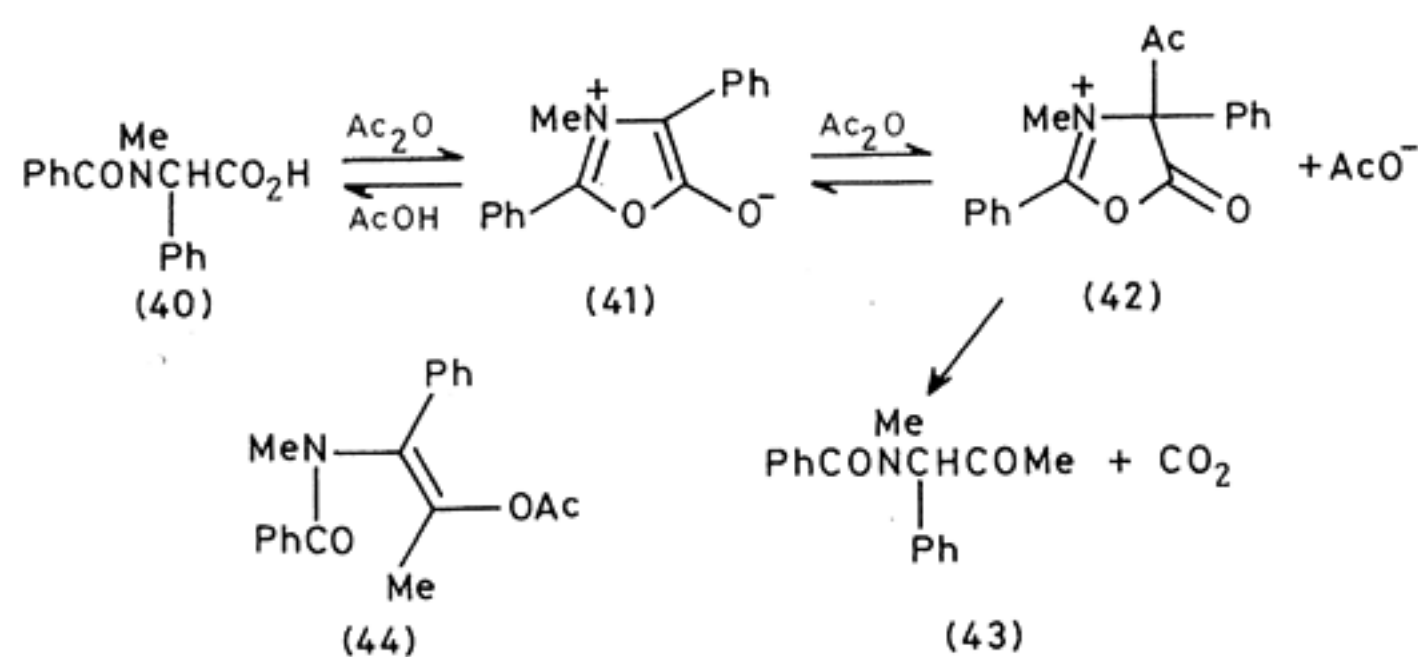
recovered (80–90%) under Dakin-West conditions. However, peptides involving secondary amino-acids react normally and the reaction was employed analytically³⁷ in identifying *N*-methylvaline as the CO₂H-terminal amino-acid in actinomycinic acid (39) (Scheme 15).



Scheme 15

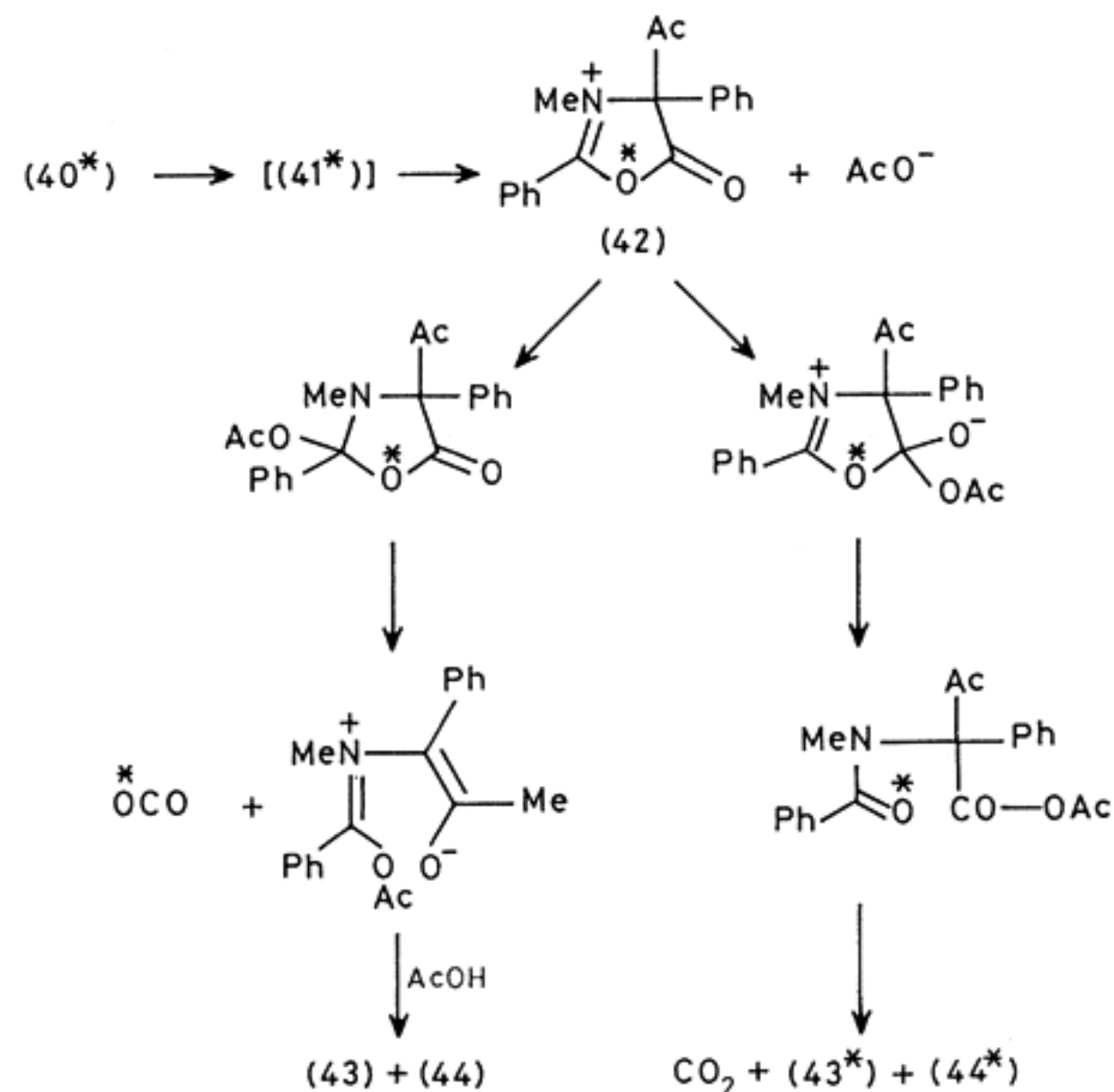
Although all of these reactions were carried out in the presence of pyridine, it has been shown that added base is unnecessary, at least for *N*-arylglycines, which yield the alkyl ketone merely by boiling with acetic or propionic anhydrides.³⁴ Similarly (37) gave the methyl ketone, but (38) proved to be inert.³⁴ This is consistent with a mechanism which includes *C*-acylation followed by decarboxylation.

Little interest has been shown in the preparative application of the reaction to secondary amino-acids, but its mechanism has received detailed attention. The oxazolinium salt (41) has been isolated under mild conditions and shown to afford the methyl ketone (43) [probably *via* (42)] when boiled with acetic anhydride (Scheme 16).^{38–40} Furthermore, Knorr and Huisgen have been able to show³⁸



Scheme 16

that, in the absence of pyridine, the course of the third step in this sequence depends on the amount of acetic acid present. Acetic anhydride containing 1.5 M acetic acid gives rise to the expected ketone (43) in up to 70% yield. However, in low concentrations of acetic acid (or in presence of pyridine) little ketone is found. The main product is the enol acetate (44), together with two pyrrole derivatives. Two routes are proposed, involving acetate attack on (42) at *both* C(2) and C(5).⁴¹ The ratio of C(2)/C(5) attack appears to be controlled by the concentration of acetic acid present, and the coexistence of these two routes has been established⁴² by the use of *N*-methyl-*N*-[¹⁸O]benzoylphenylglycine (40*), pyridine, and acetic anhydride containing known concentrations of acetic acid (Scheme 17).

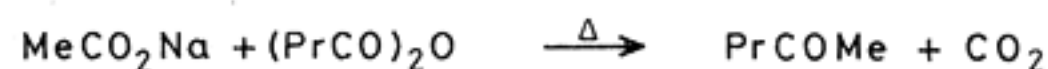


Scheme 17

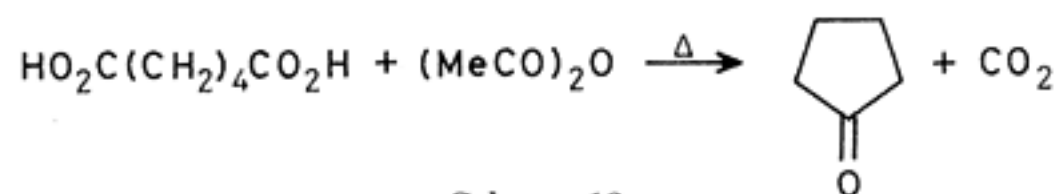
By measuring the distribution of the ¹⁸O-label in the reaction products it was concluded that at high concentrations, C(5) attack predominates but at low concentrations the C(2)/C(5) ratio is about 40:60. Complementary work, using ¹⁸O-labelled acetic anhydride³⁰ has supported this conclusion. Thus, unlike the primary amino-acid mechanism in which the oxazolone is attacked exclusively at C(5) the oxazolinium ion (42), being more electrophilic at C(2), reacts at both centres.

⁴¹ R. Knorr and G. K. Staudinger, *Chem. Ber.*, 1971, **104**, 3621.

⁴² R. Knorr, *Chem. Ber.*, 1971, **104**, 3633.



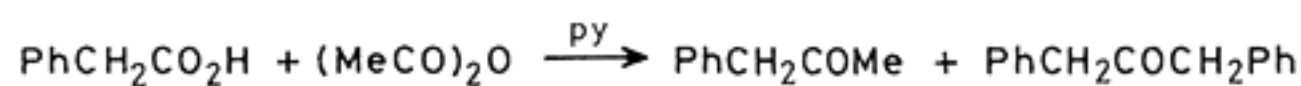
Scheme 18



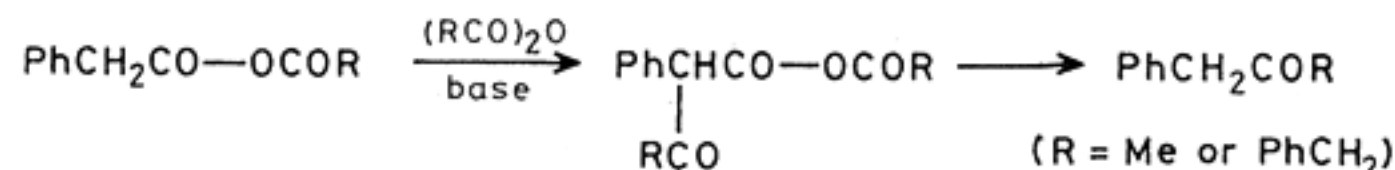
Scheme 19

4 Other Acids

In their initial paper,² Dakin and West made passing reference to the fact that some non-amino-acids, for example, chloroacetic, α -bromostearic and phenylacetic acids also yield ketones when boiled with acetic anhydride and pyridine, but they reported no experimental details or yields at that time or later. Of course, the formation of ketones from aliphatic carboxylic acid salts and anhydrides has been known since Perkin's experiments a century ago (Scheme 18),⁴³ and the same process doubtless forms the basis of the Blanc reaction⁴⁴ of certain dicarboxylic acids (Scheme 19). However, no systematic examination of the reaction was begun until much later. King and McMillan⁴⁵ showed that it is catalysed equally well by pyridine and sodium acetate but notably by tributylamine. Surprisingly, no further investigations have been reported with other organic bases. These authors also showed that the carboxylic acid involved requires at least one C(2)-H, and although the acid can be replaced by its (*sym*)anhydride, it cannot be replaced by its ester or nitrile.^{46,47} Typically, phenylacetic acid gives a moderate (56%) yield of phenylpropanone when boiled under reflux with acetic anhydride and pyridine (Scheme 20), but 1,3-diphenyl propanone is also formed as a substantial (24%) by-product⁴⁵ and, on prolonged boiling, some enol-acetylation also takes place.^{46,48} The formation of ketonic by-product is an undesirable feature of the reaction which has yet to be overcome. These ketones clearly arise from an initial acid-anhydride equilibration⁴⁹ generating phenylacetic anhydride and the mixed anhydride in addition to the (abundant) acetic anhydride. Thereafter it is generally agreed that base-catalysed acylation of these anhydrides by a second anhydride molecule leads to (two) β -ketoanhydrides and so to the ketones *via* decarboxylation (Scheme 21). In theory, the product ought also to include propanone but this is either lost on work-up or is disfavoured at the acylation step by preferential formation of the more stable benzylic anion.

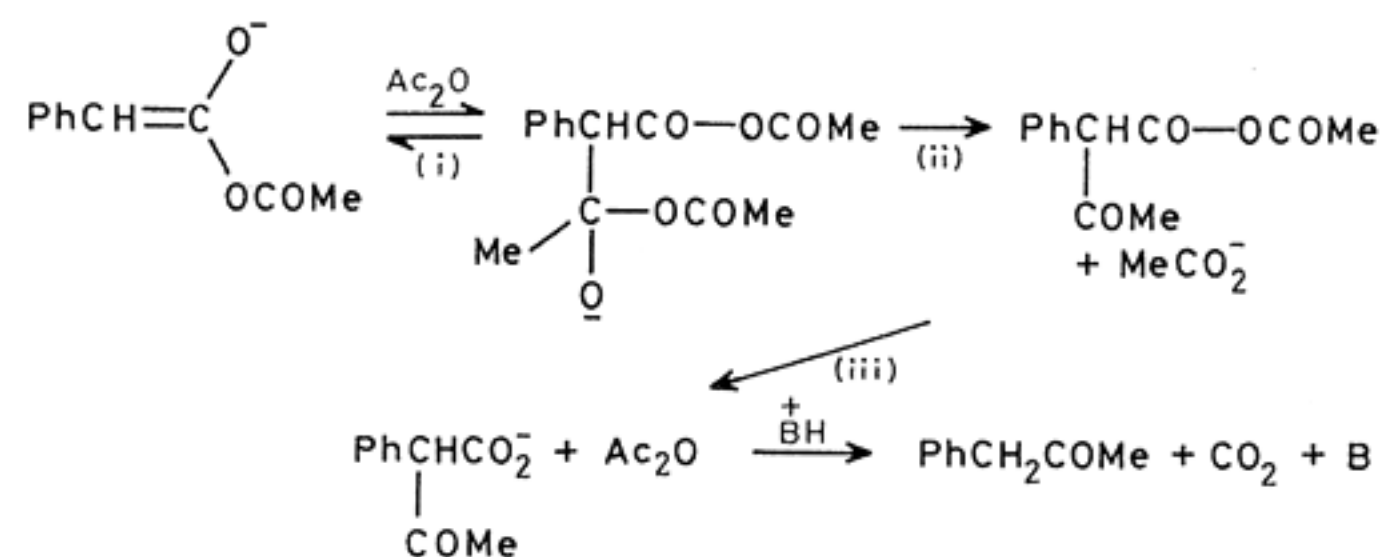


Scheme 20



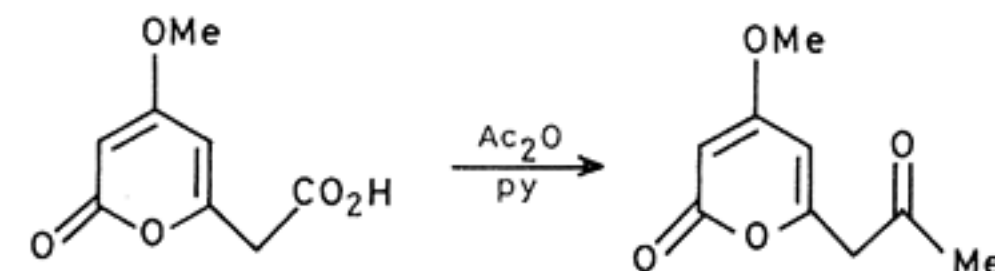
Scheme 21

However, opinions differ on the mechanism of the acylation step and a number of suggestions have been made^{45,47,50,51} including a concerted cyclic model and both inter- and intra-molecular base-catalysed C-acylations. A kinetic study⁵¹ has revealed first-order kinetics with respect to the arylacetic acid in the presence of pyridine and excess anhydride. It also revealed an isotope effect of 1.13 with (1-¹⁴C)anhydride but none with (1-¹⁴C)acid. This latter evidence casts doubt on the concerted mechanism but is consistent with Scheme 22,⁵¹ in which C-O bond breaking (step ii) is rate determining.



Scheme 22

The reaction is of practical value only with suitably 'active' α -CH groups, as in phenylacetic acid. Thus it is reported⁴⁵ that β -phenylpropanoic acid affords no ketonic product, and phenoxyacetic acid reacts slowly giving little ketone,^{46,52} but *p*-nitrophenylacetic acid reacts rapidly to give a 48% yield of methyl ketone,⁴⁶ and the highly activated pyrone (45) reacts even at room temperature (Scheme 23).⁵³ Surprisingly, no ketone appears to be produced from diphenylacetic acid,⁴⁵ perhaps because of steric effects. In the course of his strychnine synthesis⁵⁰



Scheme 23

⁴³ W. H. Perkin, *J. Chem. Soc.*, 1886, 49, 317.

⁴⁴ G. Blanc, *Comptes Rendus*, 1907, 1356; *Bull. Soc. Chim. Belg.*, 1908, 3, 778.

⁴⁵ J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 1951, 73, 4911.

⁴⁶ G. G. Smith, *J. Am. Chem. Soc.*, 1953, 75, 1134.

⁴⁷ G. L. Buchanan and J. McArdle, *J. Chem. Soc.*, 1952, 2944.

⁴⁸ W. Wunderlich, *Arch. Pharm.*, 1953, 286, 512.

⁴⁹ D. P. N. Satchell, *Quart. Rev.*, 1963, 17, 177.

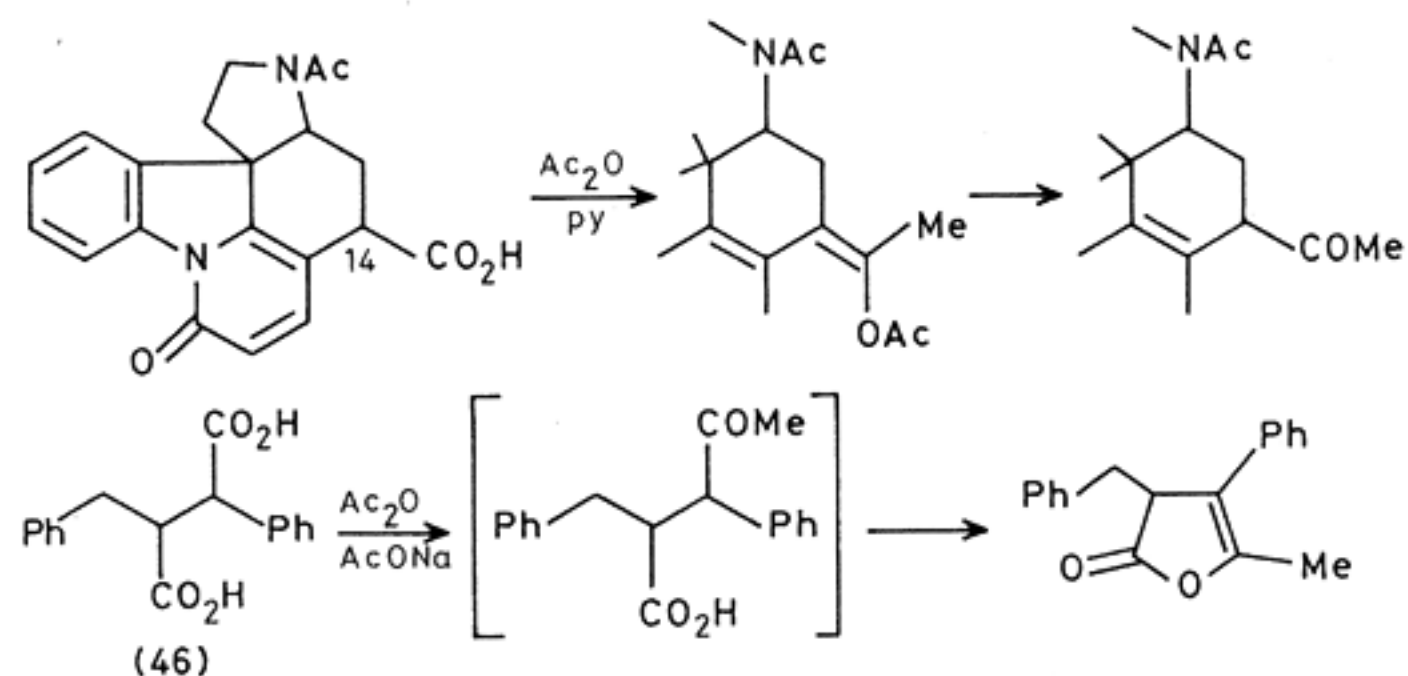
⁵⁰ R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Experientia*, 1955, Suppl. 2, 213; *Tetrahedron*, 1963, 19, 247.

⁵¹ G. G. Smith and D. M. Fahey, *J. Am. Chem. Soc.*, 1959, 81, 3391.

⁵² E. Dyer and C. E. Minnier, *J. Org. Chem.*, 1968, 33, 880.

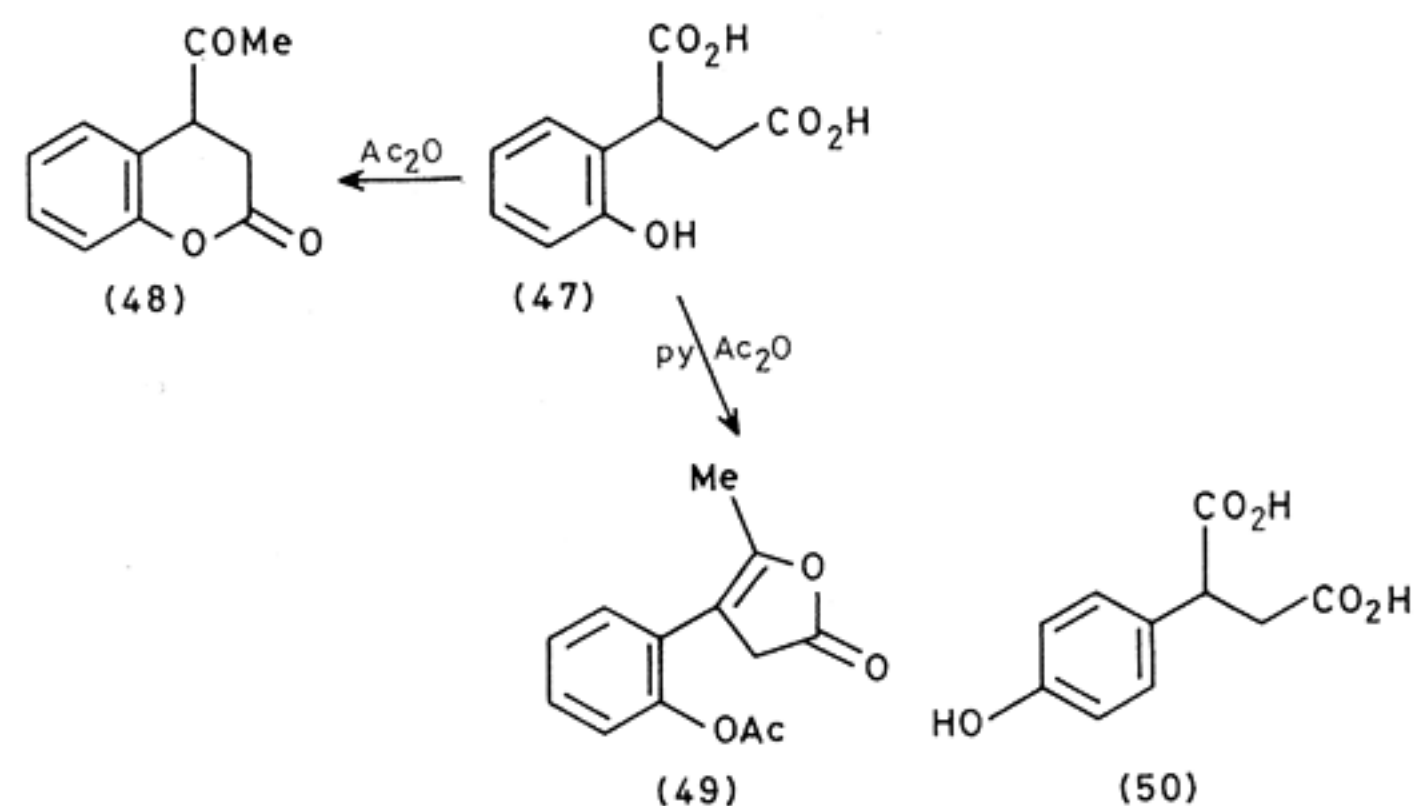
⁵³ S. Yamamura, K. Kato, and Y. Hirata, *J. Chem. Soc., Chem. Commun.*, 1968, 1580.

Woodward made use of this 'exceptionally simple method' to convert the C(14)-carboxyl group into methyl ketone during his construction of ring VI. It seems likely that the ψ -aromatic pyridone ring supplies the activation to the C(14)-H (Scheme 24).



Scheme 24

The dicarboxylic acid (46) reacts selectively⁵⁴ at the more active centre and similar selectivity was observed by Lawson¹³ in *o*-hydroxyphenylsuccinic acid (47) where reaction with acetic anhydride *alone* leads to the keto-lactone (48) (Scheme 25). In the presence of pyridine, which promotes *O*-acetylation, the reaction is again selective, yielding (49).



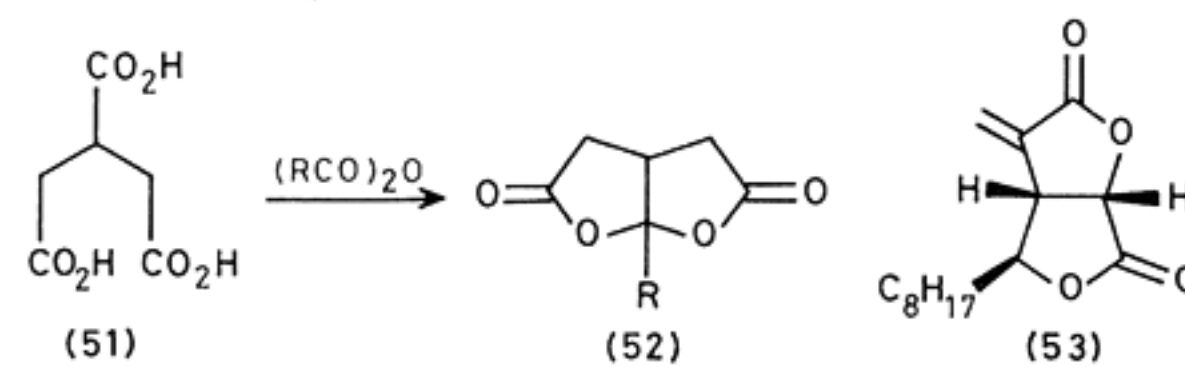
Scheme 25

Strangely, neither the *para*-isomer (50) nor phenylsuccinic acid, itself, undergo decarboxylative acetylation in the absence of a basic catalyst. This difference has received no explanation; however, Lawson has noted^{13b} that uncatalysed decarboxylative acylation is common to certain groups of succinic acids. These include *N*-benzoylaspartic acid (14) (see Section 2) whose reaction is smoother in the absence of added catalyst.¹¹ Under these reaction conditions, it has been argued, 'reaction through an intermediate oxazolone is unlikely'.^{13b}

A further example of 'uncatalysed' acylation is provided by tricarballic acid (51)^{13b} or its trisodium salt (Scheme 26).⁵⁵ Although the latter gives poorer yields, this is surely a base-catalysed reaction, for improved yields of (52) are obtained by adding powdered glass, or using glassware previously washed with a strongly alkaline detergent.⁵⁶ Decarboxylative acylation can be extended to homologues of acetic anhydride,⁴⁶ but there is evidence that yields decline as the size of the alkyl group increases.^{13,52,55} Johnson was able to overcome this shortcoming, by using the powdered glass technique described above, in his synthesis of (52) (R = C₈H₁₇), which was a key intermediate in the synthesis⁵⁶ of avenaciolide (53).

It is not difficult to accept that those carboxylic acids which incorporate a basic group, *i.e.* tertiary amino-acids, can be acylated even in the absence of pyridine. Thus the conversion (Scheme 27) of the purinylthiopropionic acid (54) into ketone (55) in substantial yield by acetic anhydride *alone*⁵² is presumably such a case, because phenylthioacetic acid gives a poor yield of ketone with acetic anhydride in the presence of 2,6-lutidine and none at all in its absence.⁵² Likewise, certain γ - and δ -t-amino-acids, *e.g.* (56), are converted into ketones by acetic anhydride alone (Scheme 28)⁵⁷ and it seems plausible that here too, the molecule carries its own catalyst. Even so, the ketonic product is formed only if R is primary. If R is secondary or benzyl the lactam (58) is formed instead, *via* the intermediate (57).

The behaviour of the *t*- α -amino-acids *N,N*-dimethylglycine (59) and its phenyl analogue (60) under Dakin-West conditions is of no preparative value, but does raise interesting mechanistic questions. These substances react with acetic anhydride, alone or in the presence of pyridine, with evolution of CO₂ but the only product to be isolated has been *N,N*-dimethylacetamide (Scheme 29).^{58,13} No reaction intermediate has ever been detected and the remainder of the reaction



Scheme 26

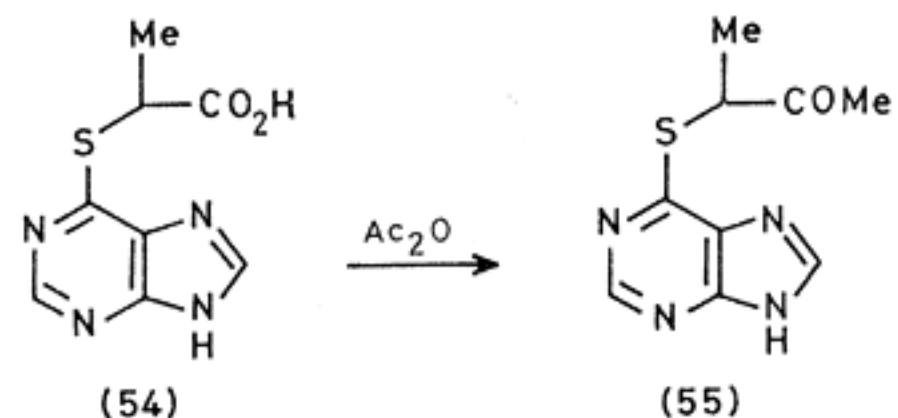
⁵⁵ R. Fittig, *Liebigs Ann. Chem.*, 1901, 314, 1.

⁵⁶ W. L. Parker and F. Johnson, *J. Org. Chem.*, 1973, 38, 2489.

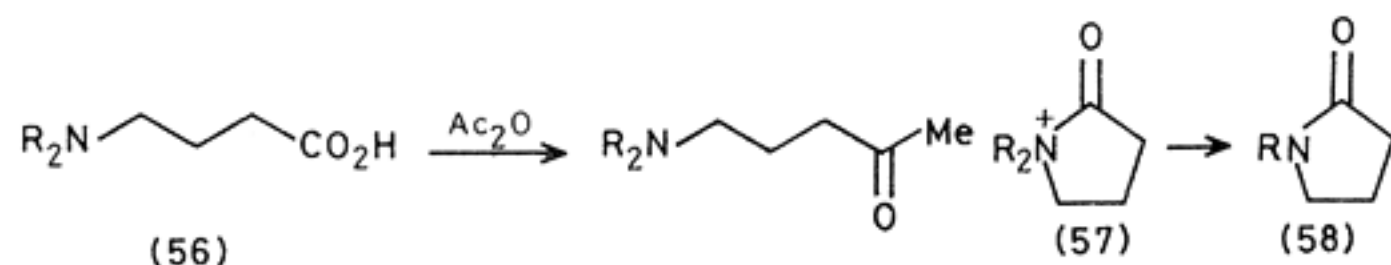
⁵⁷ P. A. Cruickshank and J. C. Sheehan, *J. Am. Chem. Soc.*, 1961, 83, 2891.

⁵⁸ J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 1951, 73, 4451.

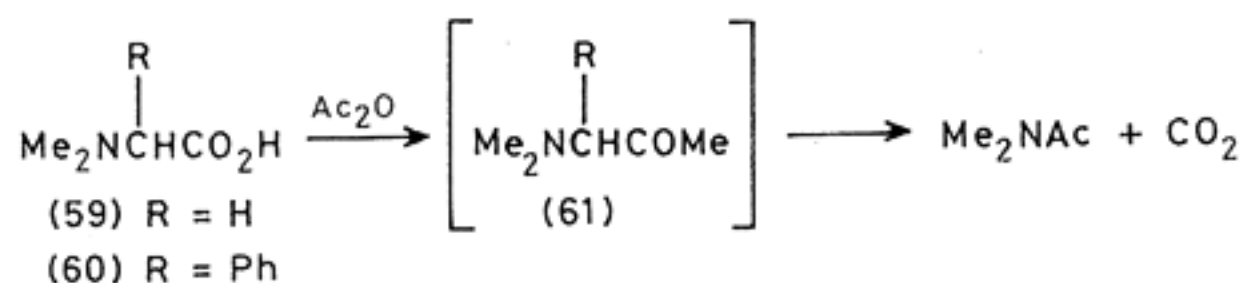
⁵⁴ R. Stoermer and H. Stroh, *Chem. Ber.*, 1935, 68, 2112.



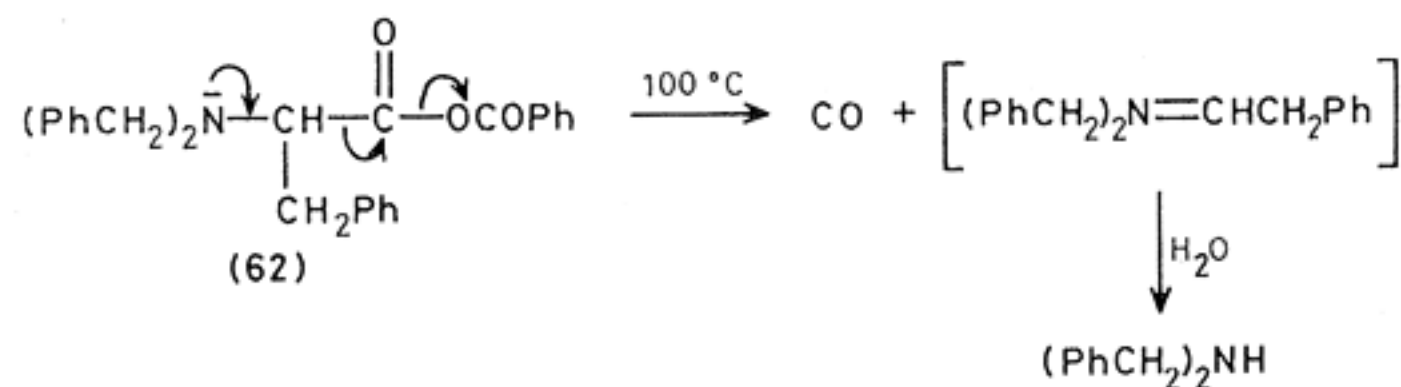
Scheme 27



Scheme 28



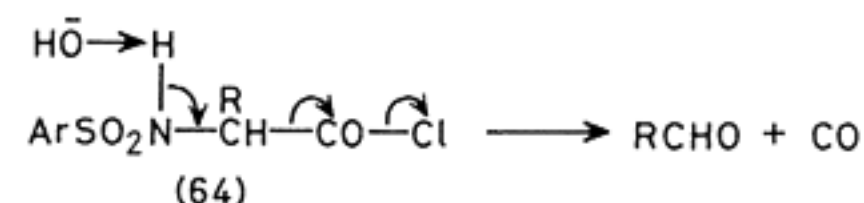
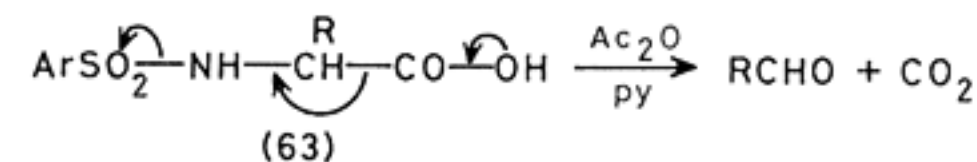
Scheme 29



Scheme 30

mixture is polymer. Nonetheless, it has been proposed⁵⁸ that *N,N*-dimethylacetamide is a decomposition product of the (hypothetical) ketone intermediate (61) and indeed, a specimen of this ketone (separately prepared) has been reported to give a 97% yield of *N,N*-dimethylacetamide when boiled with acetic anhydride.⁵⁸ Certainly, the evolution of CO₂ from (59) and (60) places them alongside (54) and (56) as self-catalysed examples of acylative decarboxylation. However, it is remarkable that the mixed anhydride (62) behaves so differently (Scheme 30), undergoing fragmentation at 100 °C with evolution of carbon monoxide,⁵⁹ for analogous mixed anhydrides might be expected to arise from both (59) and (60) under the reaction conditions.

⁵⁹ V. I. Maksimov, *Tetrahedron*, 1965, **21**, 687; *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1962, 99.



Scheme 31

Interestingly, the arylsulphonyl derivatives of α-amino-acids and their acid chlorides, (63) and (64), show a similar divergence of behaviour on treatment with base.⁶⁰ Under Dakin-West conditions the acid (63) gives rise to an aldehyde and carbon dioxide whilst the acid chloride (64) reacts with base to yield the same aldehyde accompanied by carbon monoxide (Scheme 31). Both reactions have been identified by Grob⁶¹ as examples of heterolytic fragmentation processes.

Acknowledgement. The author is grateful to Professor Frank Johnson (State University of New York at Stony Brook, N.Y., U.S.A.) for his comments and for much stimulating discussion.

⁶⁰ R. H. Wiley and R. P. Davis, *J. Am. Chem. Soc.*, 1954, **76**, 3496.

⁶¹ C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 9 and 15.

⁶² J. Lepschy, G. Höfle, L. Wilschowitz, and W. Steglich, *Liebigs Ann. Chem.*, 1974, 1753.

⁶³ R. H. Wiley, *J. Org. Chem.*, 1947, **12**, 43.

⁶⁴ A. Burger and C. R. Walter, *J. Am. Chem. Soc.*, 1950, **72**, 1988.

⁶⁵ B. M. Goldschmidt, B. L. Van Duuren, and C. Mercado, *J. Chem. Soc., (C)*, 1966, 2100.