**145.** *The Erlenmeyer Reaction with Aliphatic Aldehydes,*
2-Phenyloxazol-5-one being used instead of Hippuric Acid.

By MALCOLM CRAWFORD and W. T. LITTLE.

> Although aliphatic aldehydes do not readily undergo the Perkin reaction or its modifications the lower members will react readily with 2-phenyl-5-oxazolone and its derivatives in a type of Perkin–Erlenmeyer reaction in which neither acetic anhydride nor sodium acetate with their disturbing side reactions are present. Reaction also takes place readily with aromatic aldehydes and some ketones.

THE Erlenmeyer azlactone synthesis [1] resembles the Perkin reaction. In it an aromatic aldehyde is condensed with hippuric acid in the presence of acetic anhydride and, usually, sodium acetate. It has been suggested [2,3] that hippuric acid (I; Ar = Ph) is first converted into its azlactone, 2-phenyloxazol-5-one (II; Ar = Ph), and that it is this which condenses with the aldehyde (R·CHO) to give the unsaturated azlactone product (III; Ar = Ph).
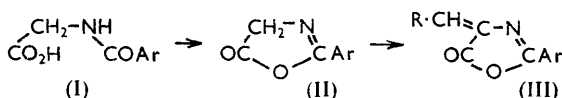
It had been assumed [4] that the intermediate (II) was unstable and isolatable only with difficulty but Russian workers [5] have described its convenient preparation in another connection. Obtained thus, in satisfactory yield, it is a yellow crystalline substance of m. p. 86° which is not very stable, presumably partly reverting to hippuric acid and partly undergoing self-condensation. Overheating during the preparation also decomposes it. It must be used within a few hours of preparation.

With aromatic aldehydes it reacts very smoothly, five minutes on the water-bath being sufficient to afford high yields of azlactones. (Sodium acetate is not required; indeed it should be avoided as it causes gum formation probably owing to rapid self-condensation). This ready reaction with aromatic aldehydes confirms the view that it is an intermediate in the Erlenmeyer reaction.

TABLE 1. *Azlactones from aromatic aldehydes and 2-phenyloxazol-5-one.*

	M. p.	Yield * (%)	Yield (%) by standard method *	Yield (%) claimed
Benzaldehyde	158°	63	58	50—80 [a]
Anisaldehyde	156	55	52	Not given [b] (*ca.* 50)
Furfuraldehyde	171	82	68	70 [c]
Cinnamaldehyde	153	72	61	Not given [d]

* Based on equimol. quantities of the reactants. Much higher yields can be obtained by using excess of either.

[a] Gillespie and Snyder, *Org. Synth.*, Coll. Vol. II, 1943, p. 489; Plöchl, *Ber.*, 1883, **16**, 2815. [b] Erlenmeyer and Wittenberg, *Annalen*, 1904, **337**, 294; Dakin, *J. Biol. Chem.*, 1910, **8**, 11. [c] Flatow, *Z. physiol. Chem.*, 1910, **64**, 367. [d] Erlenmeyer and Matter, *Annalen*, 1904, **337**, 271.

In Table 1 the yields obtained by its use from various aromatic aldehydes are compared with those obtained by the standard method with hippuric acid and those previously claimed. This method should prove useful in difficult cases. Aliphatic aldehydes are in fact examples of such difficult cases.

[1] Erlenmeyer, *Annalen*, 1893, **275**, 1.
[2] Baltazzi, *Quart. Rev.*, 1955, **9**, 151.
[3] Havinga and Spitzer, *Rec. Trav. chim.*, 1957, **76**, 173.
[4] Carter, " Organic Reactions," Wiley, New York, 1946, Vol. III, p. 214.
[5] Shemyakin, Lure, and Rodionovskaya, *Zhur. obshchei Khim.*, 1949, **19**, 769; *Chem. Abs.*, 1950, **44**, 1096.

It was shown in the preceding paper that the failure of aliphatic aldehydes to undergo the Perkin reaction is due partly to low reactivity and partly to acetate formation at high temperatures by the action of acetic anhydride and possibly aldol formation by the action of sodium acetate. Now 2-phenyloxazol-5-one appears to react in Perkin fashion in the absence of both these reagents for it behaves as an anhydride and its methylene group is so reactive that sodium acetate is unnecessary. The fact that it can react at all with aliphatic aldehydes shows that these are not inherently incapable of undergoing this type of reaction but are simply less reactive.

Normally aliphatic aldehydes do not undergo the Erlenmeyer reaction. The expected products have been obtained (though in low yield),[6] especially on use of excess of aldehyde.[7,8] Good yields have been obtained in some cases by the use of lead acetate instead of sodium acetate [9] (see Table 2, method 2). With 2-phenyloxazol-5-one alone, lower aliphatic aldehydes readily give good yields (see Table 2, method 1). The presence

TABLE 2. *Azlactone yields from aliphatic aldehydes and ketones with 2-phenyloxazol-5-one.*

	M. p.	Yield (%), Method 1	Yield (%), with lead acetate, method 2	Previous yield (%)
Ethanal	94°	46	58	20, 39 [7,9]
Propanal	84	38	55	45 [9]
Butanal	56	20	34	7—22 [9]
2-Methylpropanal	87	—	—	31 [9]
2-Ethylbutanal				
Heptanal	—	0	0	—
Octanal				
Acetone	98—99	—	35	Not given [a]
*cyclo*Hexanone	139—139·5	—	74	49 [b] Very poor

[a] Ramage and Simonsen, *J.*, 1935, 532.　[b] Boekelheide and Schramm, *J. Org. Chem.*, 1949, **14**, 298; Billimoria, Cook, and Heilbron, *J.*, 1949, 1437.

of sodium acetate again causes gum formation. Yields are improved by adding lead acetate or even acetic anhydride. Alexander [10] points out the effectiveness of a proton-donor in aiding elimination. Acetic anhydride and lead acetate may act in this capacity, as under the conditions of the reaction they will give small amounts of acetic acid. It is interesting that two of the six ketones tested reacted very well (see Table 2) (ethyl methyl ketone, diethyl ketone, acetophenone, and dipropyl ketone did not give azlactone).

Higher aliphatic aldehydes (above butanal) do not react. This failure was attributed at first to difficulties in isolating the expected azlactones. Their melting points decrease in the normal series with increasing molecular weight. To overcome this, *p*-chloro-, *p*-methyl-, and *p*-phenyl-hippuric acid were prepared. These were readily converted into their phenyloxazolones, which in turn were found also to react smoothly with the lower aliphatic aldehydes. The products from acetaldehyde and benzaldehyde had higher melting points, but none of the three oxazolones reacted with heptanal, which must therefore be considered quite unreactive, doubtless owing to the " coiling " which causes lack of reactivity in the Perkin and the Perkin–Oglialoro reaction (preceding paper).

Some of these substituted hippuric acids and intermediates may be useful in modified Erlenmeyer syntheses on account, not only of higher melting points, but also of higher yields.

[6] Erlenmeyer and Kunlin, *Annalen*, 1901, **316**, 145.
[7] Carter, Handler, and Melville, *J. Biol. Chem.*, 1939, **129**, 359.
[8] Corse, Kleiderer, and Soper, *J. Amer. Chem. Soc.*, 1948, **70**, 438.
[9] Finar and Libman, *J.*, 1949, 2726.
[10] Alexander, " Principles of Ionic Organic Reactions," Wiley, New York, 1950, pp. 181—183; see also Noyce and Snyder, *J. Amer. Chem. Soc.*, 1958, **80**, 4324.

EXPERIMENTAL

2-Phenyloxazol-5-one.—Hippuric acid (20 g.) and acetic anhydride (130 ml.) were heated on a water-bath for 20 min. with frequent shaking, then poured into benzene (200 ml.) and ice-water (200 ml.) and stirred for 30 min. The benzene layer was stirred with 1% sodium hydrogen carbonate solution (2 l.) until all acetic anhydride had been removed, washed, and dried, and the benzene was removed below 40°. The resulting solid on recrystallisation from benzene gave yellow plates (10 g.), m. p. 86°.

Reactions of 2-Phenyloxazol-5-one.—*Aromatic aldehydes.* The aldehyde (1 mol.) and 2-phenyl-oxazol-5-one (1 mol.) were heated together on the water-bath for 5 min., then poured on ice. The crystals which separated were filtered off, washed with 70% ethanol and recrystallised from ethanol. Yields and m. p.s are in Table 1.

Aliphatic aldehydes and ketones. Method 1. As the method for aromatic aldehydes gave only gums, lower temperatures and longer times were used. Propanal (1 mol.) and 2-phenyl-oxazol-5-one (1 mol.) were heated together at 50° for 3 hr. The yellow crystals obtained by pouring the mixture on ice were extracted with ether, and the extract filtered and evaporated in the presence of an equal volume of water. The pale yellow needles, m. p. 83° (38%), were recrystallised from 50% ethanol.

Method 2. Propanal (1 mol.), 2-phenyloxazol-5-one, and lead acetate (0·3 mol.) were treated together for 10 min. on the water-bath. The solid obtained on pouring the mixture on ice was washed with aqueous ethanol and recrystallised from ethanol (m. p. 84°; 55%).

Method 3. Propanal was treated as in method 2, but with acetic anhydride (3 mol.) in place of lead acetate, giving material (44%), m. p. 84°. The results by methods 1 and 2 are given in Table 2. The acetaldehyde runs were carried out in sealed bottles for longer times at room temperature.

Azlactones from 2-p-*Tolyloxazol-5-one.*—p-Toluoylglycine (5 g.), m. p. 161°, was converted into 2-p-tolyloxazol-5-one (3·2 g.) (as above), yellow plates, m. p. 101—101·5° (from benzene–ligroin). With benzaldehyde it gave 4-*benzylidene-2-p-tolyloxazol-5-one* (56%), greenish-yellow plates (from benzene–ethanol), m. p. 184·5° (Found: C, 77·8; H, 4·9; N, 5·4. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 5·0; N, 5·3%). With acetaldehyde there was obtained by method 2 but in 8 hr. at 25° a 48% yield of 4-*ethylidene-2-p-tolyloxazol-5-one*, almost colourless needles, m. p. 124—124·5° (Found: C, 71·4; H, 4·9; N, 6·9. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 7·0%).

p-Chlorobenzoylglycine (5 g.), m. p. 143°, was converted into 2-*p*-chlorophenyloxazol-5-one (2·8 g.), pale yellow needles (from ligroin), m. p. 121—122°. With benzaldehyde it gave 4-*benzylidene-2-p-chlorophenyloxazol-5-one* (80%), yellow needles (from benzene–ethanol), m. p. 179° (Found: C, 67·6; H, 3·7; N, 4·9. $C_{16}H_{10}O_2NCl$ requires C, 67·7; H, 3·6; N, 4·9%). This compound (1 g.) was refluxed with 8% sodium hydroxide solution (10 ml.) until all dissolved. On cooling, filtration, and acidification of the filtrate a white solid separated which on crystallisation from aqueous ethanol gave α-p-*chlorobenzamidocinnamic acid*, needles, m. p. 238° (Found: C, 63·7; H, 4·2; N, 4·4. $C_{16}H_{12}O_3NCl$ requires C, 63·7; H, 4·0; N, 4·6%). With acetaldehyde there was obtained by method 2, but for 20 hr. at 25°, 2-p-*chlorophenyl-4-ethylideneoxazol-5-one* (65%), needles (from ethanol), m. p. 158° (Found: C, 59·4; H, 3·8; N, 5·9. $C_{11}H_8O_2NCl$ requires C, 59·6; H, 3·6; N, 6·2%).

p-*Phenylbenzoylglycine.*—p-Phenylbenzoyl chloride, m. p. 113° (6 g.), was added gradually to glycine (5 g.) and 10% sodium hydroxide solution (50 ml.) with shaking. On acidification a solid was precipitated which on recrystallising (with charcoal) from ethanol gave the *acid* as plates, m. p. 211° (decomp.) (4·2 g.) (Found: C, 70·9; H, 5·3. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1%).

This acid (5 g.) was converted into 2-diphenylyloxazol-5-one (2·4 g.), yellow plates (from ligroin), m. p. 143° (decomp.). With benzaldehyde it gave 4-*benzylidene-2-diphenylyloxazol-5-one* (64%), yellow needles (from benzene–ethanol), m. p. 191·5—192° (Found: C, 81·8; H, 4·3; N, 4·1. $C_{22}H_{15}O_2N$ requires C, 81·2; H, 4·6; N, 4·3%). With acetaldehyde there was obtained by method 2, but for 20 hr. at 25°, 2-diphenylyl-4-ethylideneoxazol-5-one (64%), pale yellow plates (from benzene–ethanol), m. p. 122°.